Protocol COG0105

Official Title: A Pilot Synaptic Vesicle Glycoprotein 2A (SV2A) PET Study to Evaluate the Effect of CT1812 Treatment on Synaptic Density in Participants With Mild to Moderate Alzheimer's Disease

ClinicalTrials.gov ID (NCT number): NCT03493282

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Main Title

A Pilot Synaptic Vesicle Glycoprotein 2A (SV2A) PET Study to Evaluate the Effect of CT1812 Treatment on Synaptic Density in Participants with Mild to Moderate Alzheimer's Disease

Protocol Number:

COG0105

Official Short Title:

Effect of CT1812 Treatment on Brain Synaptic Density

Clinical Study Protocol

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Confidentiality Statement:

SIGNATURE PAGE FOR SPONSOR

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Approved by the following:

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SIGNATURE PAGE FOR INVESTIGATOR

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I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with all applicable regulations, ICH and the Declaration of Helsinki.

_____	_____	_____
Investigator Name	Signature	Date

1 STUDY ORGANIZATIONAL STRUCTURE

Sponsor:	Cognition Therapeutics, Inc.
Primary Sponsor Contact	[redacted]
Clinical Operations Lead	
24-Hour Medical Monitor Coverage	

2 PROTOCOL SYNOPSIS

TITLE: A Pilot Synaptic Vesicle Glycoprotein 2A (SV2A) PET Study to Evaluate the Effect of CT1812 Treatment on Synaptic Density in Participants with Mild to Moderate Alzheimer's Disease

SPONSOR: Cognition Therapeutics Inc.

PROTOCOL NUMBER: COG0105

CLINICAL STUDY PHASE: Phase Ib/2a

STUDY DRUG PRODUCT: CT1812

STUDY OBJECTIVES:

Primary:

To evaluate the safety and tolerability of CT1812 in AD patients

Secondary:

- To evaluate the effect of CT1812 on brain synaptic density in Alzheimer's disease (AD) patients using the SV2A PET ligand ^{11}C-UCB-J
- To evaluate the effect of CT1812 on cognitive and clinical outcomes in AD patients using the ADAS-Cog11 and ADAS-Cog13 (derived from ADAS-Cog14), NTB, ADCS-ADL, MMSE, CDR-SB and ADCS-CGIC
- To evaluate the effect of CT1812 on brain activity in AD patients using FDG PET and resting state functional MRI
- To evaluate the effect of CT1812 on brain volume in AD patients using volumetric MRI
- To evaluate the effect of CT1812 on CSF pharmacodynamics in AD patients through measurement of CSF Aβ 40, Aβ 42, Aβ oligomers, tau, phospho-tau, neurogranin, synpatosomal-associated protein-25 (SNAP25), synaptotagmin and NFL. Additional CSF biomarkers are listed in the statistical analysis plan.
- To evaluate the plasma and CSF concentrations of CT1812 in AD patients

Exploratory:

[redacted]

STUDY DESIGN

This is a single-center, Phase 1b randomized, double-blind, placebo-controlled parallel-group trial in adults with mild to moderate AD.

STUDY PROCEDURES

After consenting to participate in the study, screening procedures will occur between Days -60 and -1. Eligible participants will be randomized in a 1:1:1 (300 mg active: 100 mg active: placebo) ratio. The first dose of study drug will be administered in the clinic after all baseline procedures have been conducted. For the remainder of study days, participants will ingest study drug each morning at home. Participants and their study

partners will return to the clinic for repeat psychometric/neurologic testing, safety studies and PK and PD sample collection approximately 12 times during the course of the study.

Participants who prematurely discontinue the study for any reason will be asked to attend the final/ early discontinuation visit but are not required to attend a follow up visit unless deemed necessary at the discretion of the investigator.

Safety Stopping Rules:

For all participants:

The occurrence of any one of the following events will result in suspension of administration of study drug in all participants until safety information can be further reviewed by the Sponsor and Medical Monitor.

- Two occurrences of the same or similar serious adverse event (SAE) assessed as probably or possibly related to dosing with investigational product
- Two or more different participants with the same or similar severe AE assessed as probably or possibly related to dosing with the investigational product
- Four or more participants with the same or similar moderate AE which is possibly or probably related to dosing with investigational product

Under these circumstances, the Sponsor and Medical Monitor will review the available safety data and, in consultation with the study principal investigator, recommend whether dosing should continue, or if study drug administration at one of the three study doses should be terminated, or if additional monitoring procedures or safety precautions need to be employed.

If a stopping rule is achieved, selective unblinding of the participants involved may be performed by the Sponsor to determine if the SAEs/AEs are isolated to a single dose group or if they occurred in placebo participants.

The study or a dose group may also be terminated if the Medical Monitor, Study Director and Sponsor, in consultation with the lead principal investigator, determine that any adverse event(s) are occurring that are intolerable or pose a medically unacceptable safety risk.

For individual participants:

Participants who develop a severe adverse event or laboratory abnormality will not receive any additional doses and will be monitored until resolution of the AE or the return of laboratory abnormality to the acceptable screening value(s). Study drug may be re-initiated after consultation with medical monitor and sponsor. Any participant with:

- elevated ALT or AST greater than 5 X ULN should have dosing with study drug stopped and have laboratory tests repeated every 3-4 days until levels return to less than or equal to 1.5 X ULN. If the medical monitor and investigator are in agreement, study drug may be continued while a confirmatory ALT/AST is obtained within 3 days. If the confirmatory ALT/AST tests are below 5 X ULN, study drug may be continued. The frequency of the laboratory tests may be modified after discussion with the medical monitor if the liver enzymes are in a decreasing trend.
- elevated ALT or AST greater than 3 X ULN in combination with total bilirubin > 2 X ULN or INR > 1.5 X ULN OR an ALT or AST > 3 X ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) should have dosing with study drug stopped and have

laboratory testing repeated every 3-4 days. If the medical monitor and investigator are in agreement, study drug may be continued while a confirmatory laboratory testing is obtained within 3 days. If these criteria are no longer met, study drug can be continued at the discretion of the medical monitor and investigator. The frequency of the laboratory tests may be modified after discussion with the medical monitor if the laboratory tests are trending towards normal.

- An increase in serum creatinine by 0.3 mg/dL (24.4 micromol/L) or 150% of baseline that is without clinical explanation of another etiology will result in repeated serum chemistry testing within 3-7 days. If the serum creatinine elevation is confirmed on repeated testing the study drug will be discontinued. If the serum creatinine elevation resolves upon subsequent testing after study drug is discontinued the study drug may be restarted with serum creatinine monitoring at the discretion of the medical monitor and investigator.
- An increase in serum calcium to ≥10.5 mg/dl (2.63 mmol/L) that is without clinical explanation of another etiology will result in repeated serum chemistry testing within 3-7 days. If the serum calcium elevation is confirmed on repeated testing the study drug will be discontinued. If the serum calcium elevation resolves upon subsequent testing after study drug is discontinued the study drug may be restarted with serum calcium monitoring at the discretion of the medical monitor and investigator.
- Note: Fractional excretion of calcium will be monitored in each participant and interpreted in conjunction with serum creatinine and serum calcium. Given the ability of fractional excretion to fluctuate, no upper limit for discontinuing study drug based on fractional excretion of calcium has been set but it may be used as a stopping rule if persistent unexplained increases in fractional excretion of calcium are observed.

Note: Any unanticipated serious adverse events (SAEs) that are 'related' should be reported to the NIA within 48 hours of knowledge of the same.

NUMBER OF PARTICIPANTS:

Up to 25 participants

TARGET POPULATION

INCLUSION CRITERIA:

Participants may be included in the study only if they meet all of the following criteria:

1. Men, and women of non-childbearing potential, 50-85 years of age inclusively, with a diagnosis of mild to moderate Alzheimer's disease according to the 2011 NIA-AA criteria and at least a 6 month decline in cognitive function documented in the medical record.
    a. Non-childbearing potential for women is defined as postmenopausal [last natural menses greater than 24 months; in women under age 55, menopausal status will be documented with serum follicle stimulating hormone (FSH) test] or have undergone a documented bilateral tubal ligation or hysterectomy.
    b. Male participants who are sexually active with a woman of child-bearing potential must agree to use condoms during the trial and for 3 months after last dose unless the woman is using an acceptable means of birth control. Acceptable forms of birth control include abstinence, birth control

pills, or any double combination of: intrauterine device (IUD), male or female condom, diaphragm, sponge, and cervical cap.

2. Neuroimaging (MRI) obtained during screening consistent with the clinical diagnosis of Alzheimer's disease and without findings of significant exclusionary abnormalities (see exclusion criteria, number 3).
3. MMSE 18-26 inclusive.
4. A positive amyloid (e.g., Pittsburgh imaging compound B) scan at screening, or history of a positive amyloid scan prior to study entry, or prior lumbar puncture with a CSF Aβ concentration consistent with Alzheimer's disease.
5. Formal education of eight or more years.
6. Must have a caregiver who sees them at least 10 hours per week, oversees the administration of study drug, and is willing and able to oversee administration of study medication and participate in all clinic visits and some study assessments. The caregiver must provide written informed consent to participate in the study.
7. Living at home or in the community (assisted living acceptable).
8. Able to swallow CT1812 capsules.
9. Stable pharmacological treatment of any other chronic conditions for at least 30 days prior to screening.
10. Capable of providing either written informed consent or oral assent to the study procedures and for use of protected health information [Health Insurance Portability and Accountability Act (HIPAA) Authorization, if applicable]. If the Participant can provide only assent, their legally authorized representative also must provide written informed consent. Written informed consent also shall be obtained from the responsible caregiver. All consent processes must be undertaken in the presence of a witness and prior to any study procedures.
11. Must consent to apolipoprotein E (ApoE) genotyping.
12. Generally healthy with mobility (ambulatory or ambulatory-aided, i.e., walker or cane), vision and hearing (hearing aid permissible) sufficient for compliance with testing procedures.
13. Able to complete all screening evaluations.

EXCLUSION CRITERIA:

Participants will be excluded from the study if any of the following conditions apply:

1. Hospitalization or change of chronic concomitant medication within one month prior to screening.
2. Patients living in a continuous care nursing facility.
3. Screening MRI of the brain indicative of significant abnormality, including, but not limited to, prior hemorrhage or infarct > 1 cm^3, > 3 lacunar infarcts, cerebral contusion, encephalomalacia, aneurysm, vascular malformation, subdural hematoma, hydrocephalus, space-occupying lesion (e.g. abscess or brain tumor such as meningioma).
4. MRI incompatible implants and other contraindications for MRI, such as pacemaker, artificial joints, non-removable body piercings, etc. Additionally, participants who meet the following imaging exclusion criteria will not be included in this study:
    a. Claustrophobia that will result in significant anxiety and difficulty lying still for brain imaging (MRI or PET).

b. Participation in other research studies involving ionizing radiation within one year of the PET scans that would cause the participant to exceed the yearly dose limits for healthy volunteers.
c. History of intravenous (IV) drug use that would prevent venous access for PET tracer injection.
d. Severe motor problems that prevent the participant from lying still for brain imaging.
e. Severe chronic pain (e.g., as the result of rheumatoid arthritis) that would prevent them from lying still during brain imaging.

5. Clinical or laboratory findings consistent with:
   a. Other primary degenerative dementia, (dementia with Lewy bodies, fronto-temporal dementia, Huntington's disease, Jacob-Creutzfeld Disease, Down's syndrome, etc.)
   b. Other neurodegenerative condition (Parkinson's disease, amyotrophic lateral sclerosis, etc.)
   c. Seizure disorder
   d. Other infectious, metabolic or systemic diseases affecting the central nervous system (syphilis, present hypothyroidism, present vitamin B12 or folate deficiency, other laboratory values, etc.)
6. A current DSM-V diagnosis of active major depression, schizophrenia or bipolar disorder. Patients with depressive symptoms successfully managed by a stable dose of an antidepressant are allowed entry.
7. Clinically significant, advanced or unstable disease that may interfere with outcome evaluations, such as:
   a. Chronic liver disease, liver function test abnormalities or other signs of hepatic insufficiency (ALT, AST, total bilirubin > 1.5 x ULN)
   b. Respiratory insufficiency
   c. Renal insufficiency eGFR <45 mL/min based on the CKD-EPI formula [redacted] eart disease (myocardial infarction, unstable angina, heart failure, cardiomyopathy within six months before screening)
   d. Bradycardia (<45/min.) or tachycardia (>100/min.)
   e. Poorly managed hypertension (systolic >160 mm Hg and/or diastolic >95 mm Hg) or hypotension (systolic <90 mm Hg and/or diastolic <60 mm Hg)
   f. Uncontrolled diabetes defined by HbA1c >8%
8. History of cancer within 3 years of screening with the exception of fully excised non-melanoma skin cancers or non-metastatic prostate cancer that has been stable for at least 6 months.
9. Seropositive for human immunodeficiency virus (HIV).
10. History of acute/chronic hepatitis B or C and/or carriers of hepatitis B (seropositive for Hepatitis B surface antigen [HbsAg] or anti-Hepatitis C [HCV] antibody).
11. Clinically significant abnormalities in screening laboratory tests, including:
    a. hematocrit less than 33% for males and less than 30% for females
    b. absolute neutrophil cell count of 1200/uL (with the exception of a documented history of a chronic benign neutropenia), or platelet cell count of <120,000/uL
    c. international normalized ratio (INR) >1.4 or other coagulopathy, confirmed by repeat.

12. Disability that may prevent the patient from completing all study requirements (e.g. blindness, deafness, severe language difficulty, etc.).
13. Women who are fertile and of childbearing potential.
14. Within 4 weeks of screening visit or during the course of the study, concurrent treatment with antipsychotic agents (except risperidone ≤1.5 mg/day, quetiapine ≤100 mg/day, olanzapine ≤5 mg/day, and aripiprazole ≤10 mg/day), antiepileptics (except lamotrigine, gabapentin and pregabalin for nonseizure indications), centrally active anti-hypertensive drugs (e.g., clonidine, l-methyl dopa, guanidine, guanfacine, etc.), opiate analgesics, systemic corticosteroids, psychostimulants, antiparkinsonian medications (except for non-parkinsonian indications) and mood stabilizers (e.g., valproate, lithium), sedatives, and anxiolytics with the exception that use of short- to medium-acting benzodiazepines for treatment of insomnia is permitted, however, use of sedatives or hypnotics should be avoided for 8 hours before administration of cognitive tests. See Appendix A and B for a representative list.
15. Any disorder that could interfere with the absorption, distribution, metabolism or excretion of drugs (e.g. small bowel disease, Crohn's disease, celiac disease, or liver disease).
16. Nootropic drugs except stable AD meds (acetylcholinesterase inhibitors and memantine.
17. Suspected or known drug or alcohol abuse, i.e. more than approximately 60 g alcohol (approximately 1 liter of beer or 0.5 liter of wine) per day indicated by elevated MCV significantly above normal value at screening.
18. Suspected or known allergy to any components of the study treatments.
19. Enrollment in another investigational study or intake of investigational drug within the previous 30 days or five half-lives of the investigational drug, whichever is longer.
20. Previous exposure to anti Aβ vaccines.
21. Exposure to passive immunotherapies for AD (e.g. monoclonal antibodies) within the previous 180 days to dosing, and BACE inhibitors within the previous 30 days to dosing.
22. Contraindication to undergoing an LP including, but not limited to: inability to tolerate an appropriately flexed position for the time necessary to perform an LP; INR >1.4 or other coagulopathy; platelet count of <120,000/μL; infection at the desired lumbar puncture site; taking anti-coagulant medication within 90 days of screening (Note: low dose aspirin is permitted); degenerative arthritis of the lumbar spine; suspected non-communicating hydrocephalus or intracranial mass; prior history of spinal mass or trauma.
23. Use of NSAIDs more than 2 days in within any 7-day period. Each incidence of use must be recorded in the source and CRF.
24. Any condition, which in the opinion of the investigator or the sponsor makes the patient unsuitable for inclusion.
25. Intake of drugs or substances potentially involved in clinically significant CYP3A4 inhibition or induction or P-gp mediated drug interactions with CT1812, within 4 weeks or five half-lives of the interacting drug prior to administration of CT1812 and throughout the course of the study. Grapefruit juice should be avoided in the two weeks prior to dosing. See Appendix A and B for a list of these prohibited substances.

DURATION OF STUDY:

Each participant and caregiver will participate in a screening period of up to -60 days, followed by the primary double-blind treatment period of 24 weeks (169 days +/-2), followed by an optional double-blind treatment period of an additional 24 weeks (337 days +/-2). A follow up visit will occur 2 weeks after completion of dosing. Including the Screening period of 60 days, the total duration of participant participation in the study is up to 36 weeks for those undergoing the first six months of treatment and the follow up visit only and up to 60 weeks for those undergoing both six month double blind treatment periods. If a delay occurs with subjects progressing from the primary study to the extension study, a maximum of 4 weeks will be permitted. It is anticipated that enrollment will occur over 15 months and all protocol activities will be completed after 21 months, with an additional 3 months for data analysis.

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3 GLOSSARY OF TERMS AND ABBREVIATIONS

Abbreviation	Description
Abeta	amyloid beta
Aβ	amyloid beta
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale – cognition subscale
ADCS-ADL	Alzheimer's Disease Cooperative Study – Activities of Daily Living
ADCS-CGIC	Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change
AE	adverse event
ALT	alanine aminotransferase
ApoE	gene which codes for apolipoprotein E
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
β-HCG	beta human chorionic gonadotropin
BACE	beta secretase cleaving enzyme
B_{max}	total density of receptors
BMI	body mass index (kg/m^2)
BP	systolic and diastolic blood pressure
BP_{ND}	binding potential non-displaceable
BUN	blood urea nitrogen
C	Celsius
CDR-SB	Clinical Dementia Rating Scale Sum of Boxes
CFT	Category Fluency Test
CL/F	apparent systemic clearance of drug after an oral dose
CMC	Chemistry, Manufacturing and Control
C_{max}	maximum plasma concentration
CNS	central nervous system
COWAT	Controlled Word Association Test
CPK	creatine phosphokinase
CRF	case report form
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	cytochrome P450
dL	deciliter
DDI	drug-drug interaction
DMF	Drug Master File
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate

EOS	end of synthesis
F	Fahrenheit
FDA	Food and Drug Administration
^{18}F-FDG	2-deoxy-2-[fluorine-18]fluoro- D-glucose
FSH	follicle stimulating hormone
fMRI	functional magnetic resonance imaging
GCP	Good Clinical Practice
GDS	Geriatric Depression Scale
h	hour(s)
HbA1c	glycosylated hemoglobin
HBsAg	hepatitis B surface antigen
HCI	hypometabolic convergence index
HCV	hepatitis C virus
hERG	human Ether-à-go-go Related Gene
Hgb	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HPLC	high pressure liquid chromatography
IC_{50}	half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
INR	international normalized ratio
IRB	Institutional Review Board
IUD	intrauterine device
Kd	dissociation constant
kg	kilogram
KIM-1	kidney injury molecule -1
LDH	lactate dehydrogenase
LP	lumbar puncture
MAD	multiple ascending dose
MCI	mild cognitive impairment
MCV	mean corpuscular volume
µg	microgram
mg	milligram
mL	milliliter
mM	millimolar
MMSE	Mini Mental State Exam
MTD	maximum tolerated dose
NFL	neurofilament light
NSAID	non-steroidal anti-inflammatory drug

NTB	Neuropsychological Test Battery
OATP1B1	organic anion transporter polypedtides
PD	pharmacodynamics
PDF	Portable Document Format
PET	Positron emission tomography
P-gp	permeability glycoprotein
PK	pharmacokinetic
PGRMC1	progesterone receptor membrane component 1
PT	prothrombin time
QD	once daily
ROI	region of interest
SAE	serious adverse event
SNAP25	synaptosomal-associated protein 25
SV2A	synaptic vesicle glycoprotein 2A
$t_{1/2}$	terminal half life
TK	toxicokinetic
T_{max}	time to maximum concentration
ULN	upper limit of normal
USP	United States Pharmacopeia
Vz/F	apparent volume of distribution in the terminal phase after an oral dose

4 INTRODUCTION

4.1 Background

Synaptic dysfunction and loss caused by age-dependent accumulation of synaptotoxic beta-amyloid (Abeta, Aβ) 1-42 oligomers is proposed to underlie cognitive decline in Alzheimer's disease (AD). Accumulation of Aβ protein leads to self-association, resulting in formation of oligomers. Cognition Therapeutics Inc. has demonstrated that Aβ oligomers bind saturably to a single high affinity site on the surface of neuronal synapses (Izzo et al, 2014a, b). Once bound, these oligomers alter membrane trafficking rate and reduce surface expression of neuronal receptors critical for synaptic plasticity (Hsieh, 2006). This leads to failure of long-term potentiation, reversible spine loss in neurons, and impaired cognitive performance that progress throughout the course of AD (Shankar, 2007; Zempel, 2013). Cognition Therapeutics Inc. has identified a receptor not previously associated with AD that mediates the binding of Aβ oligomers to neurons, the sigma-2/ progesterone receptor membrane component 1 (PGRMC1) receptor (Izzo et al, 2014a, b).

Cognition Therapeutics has discovered a series of highly brain penetrant, novel sigma-2/PGRMC1 antagonist molecules, including CT1812 that both prevent and competitively displace oligomer binding at neuronal synapses, prevent and reverse spine loss in neurons and prevent and treat oligomer-induced deficits in membrane trafficking *in vitro*. These antagonists displace endogenous human AD patient oligomers from brain tissue sections in a dose-dependent manner. Chronic administration of sigma-2/PGRMC1 antagonists at doses that reach brain concentrations corresponding to greater than 80% estimated receptor occupancy at the sigma-2/PGRMC1 receptor restore cognitive function in aged transgenic hAPP Swe/Ldn mice models of AD. These molecules work by allosteric antagonism of the sigma-2/PGRMC1 receptor protein or a protein closely associated with it to modulate oligomer binding site affinity, representing a novel previously unrecognized mechanism of action for disease-modifying Alzheimer's therapeutics.

CT1812 is a highly brain penetrant novel sigma-2/PGRMC1 antagonist molecule that prevents and displaces binding of Aβ 42 oligomers to receptors on brain cells, and clears the Aβ 42 oligomers into the cerebrospinal fluid (CSF). *In vitro*, in cultured rat neurons, CT1812 not only antagonizes binding of Aβ 42 oligomers, but also prevents Aβ a oligomer-induced membrane trafficking changes. Chronic treatment with this first-in-class, highly brain-penetrant, disease-modifying oligomer receptor antagonist restores aged AD model transgenic mouse performance to normal in multiple cognitive tests. Sponsor hypothesizes that chronic treatment with CT1812

could restore neuronal plasticity compromised by Aβ oligomers, and thus improve cognitive function in patients throughout the course of AD. In aged AD transgenic mice, CT1812 causes displacement of Aβ oligomers into the interstitial fluid of the hippocampus and displacement of the Aβ oligomers in the CSF. This approach is fundamentally different than that of other therapeutics in development (such as beta secretase cleaving enzyme [BACE] inhibitors) that focus on lowering the brain concentrations of beta amyloid protein. This product could provide the first clinical test of the hypothesis that cognitive decline in AD is related to toxic effects of Aβ oligomers on synaptic function.

^{11}C-UCB-J, is a positron emission tomography (PET) tracer for quantitative synaptic vesicle glycoprotein 2A (SV2A) imaging *in vivo*. In nonhuman primates (Nabulsi et al, 2016), tracer uptake was high in gray matter, consistent with the ubiquitous expression of SV2A. Pretreatment with levetiracetam (Keppra®), an anticonvulsant that binds specifically to SV2A22-24, induced 60-90% occupancy, and self-block with unlabeled UCB-J yielded an *in vivo* dissociation constant (Kd) of 3.4 nM with a total density of receptors (B_{max}) of 150-400 nM, in agreement with *in vitro* values (Gillard et al, 2006). Further, there was no evidence of specific binding in white matter. Also, in baboon, we found excellent correlation between *in vivo* PET SV2A measures and *in vitro* Western blot assays of SV2A and synaptophysin, a widely used synaptic marker, as well as with SV2A homogenate binding data (Finnema et al, 2016).

Recently, we carried out first-in-human studies, and ^{11}C-UCB-J had high brain uptake (peak SUV: ~10), yielding high quality images of volume of distribution (VT) with excellent reproducibility (Finnema et al, 2016). Preliminary results in mild cognitive impairment (MCI) and AD show specific reductions, most pronounced in the hippocampus. Thus, based on our pilot data, ^{11}C-UCB-J is an excellent tracer for quantitative imaging of SV2A in the human brain and we thus hypothesize that ^{11}C-UCB-J PET can be used as an *in vivo* biomarker of synaptic density loss in AD. As a direct measure of synaptic density, SV2A imaging has the potential to be more reliable and diagnostically useful than ^{18}F-FDG, i.e., a better marker of AD progression.

There are no currently approved products for the treatment of AD that function by blocking the binding and pathological activity of soluble Abeta oligomers. While there are some approved drugs for other indications that demonstrate significant affinity at sigma-2/PGRMC1 receptors, unlike CT1812, these other drugs have significant activity at other pharmacological targets besides the sigma-2/PGRMC-1 receptor, which would make them undesirable therapeutic agents for this indication. None of these have been tested or approved for treating AD or cognitive impairment.

4.2 Nonclinical Experience

4.2.1 Nonclinical Pharmacology Studies

CT1812 is a lipophilic isoindoline formulated as a fumarate salt, and is the result of a structure-based medicinal chemistry optimization program comprised of over 300 analogs. CT1812's properties are fully described along with all preclinical studies in the Investigator Brochure. CT1812 has a high affinity at the target receptor sigma-2/PGRMC1 (S2), and is >100-fold selective for this receptor over other receptors and ion channels. Dose-limiting toxicities at higher doses in both species appear to be hypercalcemia and renal tubular damage, both of which are non-invasively monitored via measurement of serum calcium and urinary markers of renal tubular injury such as kidney injury molecule 1 (KIM-149,50).

In vitro pharmacodynamic (PD) studies confirmed CT1812 target binding specificity, affinity and engagement, including the prevention and reversal of Aβ oligomer binding and the prevention of Aβ oligomer-induced synapse loss.

In vivo PD studies confirmed the desired consequences of target engagement, including cognitive improvements in an aged transgenic mouse model of AD following oral administration of an apparently tolerated dose of CT1812 daily for 9 weeks. Additional *in vivo* PD studies, using an Aβ oligomer detecting microelectrode in an aged transgenic mouse model of AD, demonstrated that administration of CT1812 caused an acute increase in soluble Aβ oligomers in the interstitial fluid of the hippocampus and a sustained increased in soluble Aβ oligomers in the CSF of the lateral ventricle of the brain. These increases in soluble Aβ oligomers occurred without a change in the amount of soluble Aβ 1-40, indicating that displacement of Aβ oligomers occurred following treatment with CT1812.

4.2.2 Nonclinical Pharmacokinetic Studies

Absorption of CT1812 following oral gavage administration to mice, rats and dogs appears to be very rapid, with brain concentrations exceeding those concurrently measured in plasma. The drug is highly protein-bound in plasma from rat, mouse, dog, and human, but only weakly bound to blood cells. Systemic exposures to CT1812 following oral administration to rats and dogs were greater than dose-proportional at high, toxicologically relevant dosages. Extensive first-pass metabolism appears to be via oxidation and/or direct glucuronidation.

Studies with human recombinant cytochrome P450 (CYP) isoforms show rapid metabolism ($t_{1/2}$ of 6.8 min) by CYP3A4, and slower metabolism ($t_{1/2}$ of 57 and 81 minutes) by CYP2D6 and

CYP2C19. A direct glucuronide conjugate was also observed *in vitro* in human hepatocyte incubations, consistent with that observed *in vivo* in rats and dogs.

CT1812 was not an inhibitor of CYP1A2, CYP2B6 or CYP2C8, with less than 50% inhibition of activity observed at the highest concentration evaluated (10 µM). CT1812 was a weak inhibitor of CYP2C9, CYP2C19, CYP2D6, and CYP3A4, with half maximal inhibitory concentration (IC_{50}) values ranging from 4.4 to 38 µM. However, when evaluated in the context of systemic exposure data in humans, the drug-drug interaction liability from these effects was considered to be minimal. CT1812 was found to be an inducer of CYP3A4 (≥0.3 µM), suggesting a potentially clinically significant risk of drug-drug interactions (DDI) with this isoform, but induction of CYP2B6 and CYP1A2 appear less likely. CT1812 does appear to be a substrate for p-glycoprotein (P-gp), and inhibits P-gp with an IC_{50} of 10 µM. This is considered to be potentially clinically significant, primarily due to the possibility of interactions in the gastrointestinal (GI) tract. *In vitro* inhibition of the OATP1B1 transporter (IC_{50} of 11.5 µM) by CT1812 does not appear to be clinically relevant, when evaluated in the context of systemic exposure data in humans. As assessed per the FDA 2012 draft guidance for DDI evaluations, clinically relevant DDI are suggested via CT1812 effects on CYP3A4 and p-glycoprotein (P-gp).

4.2.3 Nonclinical Safety Studies

Two hERG (human Ether-à-go-go Related Gene) assays were performed to assess effects of CT1812 on the rapidly activating delayed rectifier potassium channels (IKr) using channels stably transfected and over-expressed in Chinese Hamster Ovary cells. Using whole-cell patch clamp electrophysiology, CT1812 was tested in both studies in duplicate at concentrations of 1, 3, 10, and 30 µM. Mean IC_{50} values of 26 µM and 0.6 µM were determined in the first and second assay, respectively. Reasons for the differing results are unknown. However, no ECG effects were noted in the telemeterized dog cardiovascular safety study or in the multiple-dose dog pivotal toxicology study when tested up to high-dose mean maximum plasma concentration (C_{max}) values of approximately 4 µM.

Safety pharmacology studies with rats revealed no apparent effects on (central nervous system (CNS) or pulmonary parameters following single oral dosages that exceeded the maximum tolerated dose in this species.

General toxicology studies with rats and dogs following oral dosing of CT1812 revealed dose-limiting toxicity that manifested as degenerative changes in the proximal tubules of kidney, hypercalcemia, and vascular mineralization and/or degeneration involving multiple tissues and

organs in each species. Tolerable and intolerable dosages and exposures, characterized with each species, informed the selection of dosages for this trial.

Genetic toxicology studies revealed no positive responses in bacterial and mammalian *in vitro* assays, or in an *in vivo* mouse bone marrow micronucleus assay when tested up to maximally feasible dosages.

4.3 Clinical Experience

CT1812 has been administered safely with good tolerability in over 60 healthy volunteers in a placebo-controlled Phase 1a trial (COG0101). Six single and three multiple dose cohorts (QD, 14 days) were observed under close inpatient stay (N=6-8 treated, 2 placebo per cohort). Plasma concentrations of drug were shown to be approximately dose proportional across two orders of magnitude [0.13-14.93 mg (free base equivalent)/kg], and accumulation was minimal. Peak concentrations of CT1812 were reached within 1 to 2 hours and the plasma half-life was shown to be approximately 12 hours. Adverse events were mostly mild to moderate in severity and principally included headache, nausea, vomiting, diarrhea, constipation, abdominal pain, dyspepsia, upper respiratory tract infection, lightheadedness, syncope, myalgia, dizziness, rash and pain at the lumbar puncture site in those subjects who had lumbar punctures. There was only one AE of severe intensity, being an SAE of upper respiratory tract infection, occurring in one subject in the 840 mg dose of the multiple ascending dose (MAD) study, believed to be unrelated to study drug based on a similar pattern of URTIs in subjects receiving drugs other than CT1812 in the study unit during the same time period. One subject in the multiple dose cohort study developed a rash while on study drug. This subject showed improvement after discontinuing CT1812.

No evidence of renal toxicity has been observed to date based on routine measures of renal function (serum creatinine, blood urea nitrogen [BUN]) or cystatin C.

Four subjects in the MAD study showed an increase in liver function tests below 3X the upper limit of normal (including one subject on placebo). Subsequent studies will closely monitor liver enzyme parameters to determine if these were sporadic findings or possibly drug-related.

In COG0103 15 healthy volunteers evaluated potential effects of CT1812 on the disposition of sensitive substrates of selected CYP isoenzymes CYP2C19 (omeprazole), CYP2C9 (tolbutamide), CYP2D6 (dextromethorphan), and CYP3A4/5 (midazolam). Subjects were administered the probe drugs on Day -2 and pharmacokinetic (PK) evaluations performed. On Days 1 through 6, each subject took CT1812 560 mg. The CT1812 dose on Day 6 was taken

concomitantly with the probe drug cocktail, and PK evaluation was conducted. No significant interaction was observed for isoenzymes 2C19 and 2C9. A weak drug interaction was observed between steady-state CT1812 and midazolam 4 mg (CYP3A4). Midazolam area under the concentration-time curve $(AUC)_{last}$ and the AUC_{last} ratio (parent to metabolite) decreased by 24% and 28%, respectively, when midazolam 4 mg was taken with steady state CT1812 than when midazolam was taken alone. A weak drug interaction was observed between steady-state CT1812 and dextromethorphan 50 mg (CYP2D6), as indicated by a 1.75-fold and 2-fold increase in dextromethorphan AUC_{last} and C_{max}, respectively, following the combination treatment relative to dextromethorphan alone; however, the dextromethorphan/dextrorphan AUC_{last} ratio was similar between treatments. Based on the small magnitude of the interactions observed in this study for the isoenzymes CYP2D6 and CYP3A4, clinically meaningful implications are unlikely.

A Phase 1a/2 trial (COG 0102) has completed enrollment in Australia, evaluating the safety and pharmacokinetics of three doses of once a day CT1812 (90 mg, 280 mg, 560 mg) dosed for 28 days in subjects with mild to moderate Alzheimer's disease. This study enrolled 19 subjects in a 1:1:1:1 ratio of these doses vs. placebo. In general, all doses were relatively well tolerated, with no SAEs. All AEs were considered mild or moderate. While there was an increased frequency observed in total AEs with increasing dose, the small number of treated subjects does not permit definitive conclusions regarding the incidence of AEs by dose in a larger study population. Specific AEs which were noted to occur with greater frequency at the 560 mg dose included transient lymphocytopenia, nausea, vomiting, headache, fatigue, and depression. These AEs resolved in most instances while treatment was ongoing; one subject at the 560 mg dose experienced an ALT increase of 4.7 X ULN which resolved to normal levels after discontinuation of study drug. Cognitive outcomes were similar across the treatment groups. Plasma CT1812 concentration increased approximately dose proportionally, with a dose dependent increase in CSF concentration. CSF concentrations at all tested doses were > 80% of estimated brain PGRMC-1 receptor occupancy, which was the threshold associated with efficacy in preclinical studies.

4.4 Rationale for Study

This pilot trial project proposes to evaluate the effect of CT1812 on synaptic density and cognitive function in a Phase 1b randomized clinical trial in AD patients. By combining measurements of cognitive function with novel PET imaging of synaptic density in the same patients, this trial can directly test the mechanism of action of CT1812 and the Aβ oligomer hypothesis of AD (Finnema et al., 2016). CT1812 is an orally administered lipophilic isoindoline, formulated as a fumarate salt, that is rapidly absorbed and highly brain penetrant. Cognition Therapeutics Inc. discovered

this mechanism of action along with the role of sigma- 2/PGRMC1 in AD, as well as drug candidates that have the potential to rapidly restore synapses and improve symptoms and to attenuate clinical progression of the illness ([redacted]). Thus, the long-term development plan for these drug candidates includes pilot, early and late clinical development trials that evaluate the potential for both symptom improvement (months) and long-term disease modification (>year).

4.5 Rationale for Selected Dose

Based on brain receptor occupancy studies in animals, the daily dose of 300 mg/day is projected to exceed 95% occupancy while the 100 mg/day dose is projected to exceed 80% receptor occupancy. In the Phase 1 multiple dose 2-week trial, doses exceeding 300 mg/day were well-tolerated in both younger (≤64 years of age) and older (≥65 years of age) participants. In the phase 1 AD trial tolerability was also acceptable with no severe or serious adverse events observed at doses exceeding 300 mg/day.

5 STUDY OBJECTIVES

5.1 Primary Objective

- To evaluate the safety and tolerability of CT1812 in AD patients

5.2 Secondary Objectives

- To evaluate the effect of CT1812 on brain synaptic density in AD patients using the SV2A PET ligand ^{11}C-UCB-J.
- To evaluate the effect of CT1812 on cognitive and clinical outcomes in AD patients using the ADAS-Cog11 and ADAS-Cog13 (derived from ADAS-Cog14), NTB, ADCS-ADL, MMSE, CDR-SB, and ADCS-CGIC
- To evaluate the effect of CT1812 on brain activity in AD patients using FDG PET and resting state functional MRI
- To evaluate the effect of CT1812 on brain volume in AD patients using volumetric MRI
- To evaluate the effect of CT1812 on CSF pharmacodynamics in AD patients through measurement of CSF Aβ 40, Aβ 42, Aβ oligomers, tau, phospho-tau, neurogranin, synpatosomal-associated protein-25 (SNAP25), synaptotagmin and NFL. Additional CSF biomarkers are listed in the statistical analysis plan.
- To evaluate the plasma and CSF concentrations of CT1812 in AD patients

5.3 Exploratory Objective

- To correlate changes in synaptic density, other imaging endpoints and biomarkers, with cognitive function following CT1812 treatment.
- To evaluate the plasma CT1812 metabolites in AD patients

6 STUDY TYPE AND DESIGN

6.1 Study Type

This is a single-center, Phase 1b, randomized, double-blind, placebo-controlled, parallel-group trial in adults with mild to moderate AD.

6.2 Endpoints

6.2.1 Primary Endpoint

Safety Endpoints

- The incidence and severity of adverse events (AE)
- The incidence of serious adverse events (SAE)
- Changes in vital signs
- Changes in physical and neurological exam findings
- Changes in body mass
- Changes in electrocardiogram (ECG) findings
- Changes in clinical laboratory testing (serum chemistry, hematology, urinalysis)
- Changes in the Columbia Suicide Severity Rating Scale (C-SSRS)

6.2.2 Secondary Endpoints

The primary imaging endpoint is the change from the baseline in synaptic density as measured by differences in SV2A PET ligand ^{11}C-UCB-J uptake after dosing with CT1812 versus placebo.

Cognitive and clinical outcomes:

- Mini Mental State Exam (MMSE).

- Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) 11 and ADAS-Cog13 (delayed recall and Number Cancellation added to ADAS-Cog11 in the ADAS-Cog13); ADAS-Cog14 includes the maze added to ADAS-Cog13.
- Neuropsychological Test Battery (NTB) including Trails A and B, Digit Span, and Letter and Category Fluency (CFT).
- Alzheimer's Disease Cooperative Study (ADCS)-Clinical Global Impression of Change (CGIC).
- ADCS-Activities of Daily Living (ADCS-ADL).
- Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB)
- Composite z-score scales (Cognitive Composite score; Memory composite score; Attention composite score; Executive Function composite score).
- Imaging Outcomes
    - FDG PET
    - Functional MRI
    - Volumetric MRI
- CSF pharmacodynamics in AD patients through measurement of CSF Aβ 40, Aβ 42, Aβ oligomers, tau, phospho-tau, neurogranin, SNAP25, and NFL.

6.2.3 Pharmacokinetic Endpoints

The following CT1812 pharmacokinetic assessments will be made based on serial pre-dose concentrations in plasma and CSF:

- CT1812 CSF/plasma concentration ratio
- Changes in pre-dose CT1812 plasma concentrations
- Plasma CT1812 metabolites

6.3 Study Design

After consenting to participate in the study, screening procedures will occur between Days -60 and -1. Eligible participants will be randomized in a 1:1:1 (300 mg active: 100 mg active: placebo) ratio. The first dose of study drug will be administered in the clinic after all baseline procedures have been conducted. For the remainder of study days, participants will ingest study drug each morning at home. Participants and their study partners will return to the clinic for repeat psychometric/neurologic testing, safety studies, and PK and PD sample collection approximately every 2 weeks for the first 6 weeks and then every 3 weeks thereafter up to 24 weeks for the

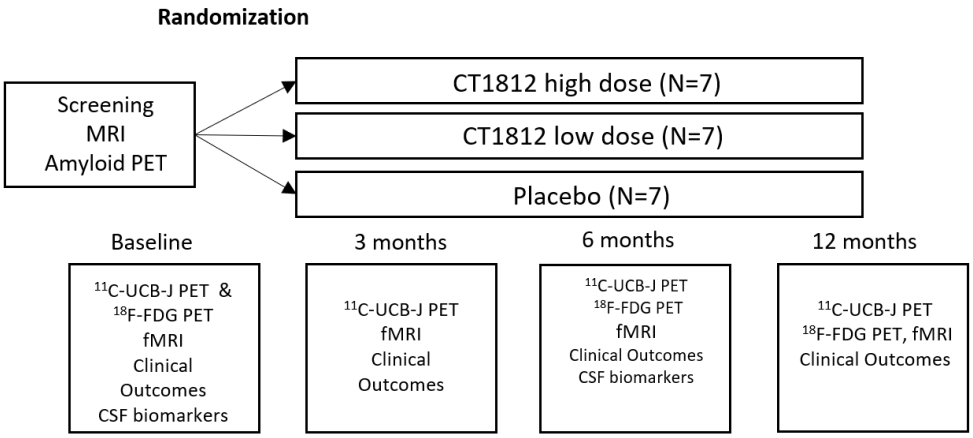
primary study followed by an optional double-blind extension treatment period of an additional 24 weeks (337 days +/-2).as well as a follow up visit at 2 weeks after the final treatment visit.

Participants who prematurely discontinue the study for any reason will be asked to attend a final safety and efficacy visit.

6.4 Schematic Study Design

The study design schematic is shown in Figure 1.

Figure 1 - Schematic Study Design



7 STUDY DRUG

7.1 Supply and Storage

CT1812 will be provided to the site pharmacy as a hydroxypropyl methylcellulose (HPMC) capsule containing 191 mg or 64 mg mg of CT1812 fumarate salt (equivalent to 150 mg or 50 mg of the CT1812 free base, respectively). Study drug will be provided in amber colored, induction sealed, screw-top bottles with desiccant packs. All study drug (unopened and opened bottles) will be stored between 2-8 degrees Celsius.

Placebo capsules (containing of 191 mg or 64 mg of lactose monohydrate) will be supplied to match the CT1812 supplies in the same packaging and will require the same storage conditions (i.e., between 2-8 degrees Celsius).

Due to the short half-life, PET drugs are prepared and formulated immediately before administration, and therefore there are no issues with storage or stability. PET drug products are stored at room temperature and are stable for at least 60 min after preparation.

The preparation of sterile PET drug products is validated prior to human use. Sterility is achieved by passing the PET drug product through a 0.22 micron membrane filter during the last step of the formulation process. Prior to release for administration, a bubble point test is performed on the membrane filter used for terminal sterilization in order to validate and verify its integrity during the filtration process. Due to the short half-life, a sample of the PET drug product is tested for sterility after administration for further confirmation.

The level of endotoxin in each batch of the final PET drug product is determined quantitatively prior to release for administration using the Food and Drug Administration (FDA) approved Charles River Laboratory's Portable Testing System (Endosafe®-PTS).

The PET drug (radiotracer) will be prepared at the Yale PET Center in accordance with local Chemistry Manufacturing & Control (CMC) procedures and quality specifications described in local Drug Master File (DMF), both of which will be submitted to the FDA for approval. Briefly, ^{11}C-UCB-J is radiolabeled by C–[^{11}C]methylation of the boronate precursor with [^{11}C]methyl iodide ([^{11}C]MeI) according to the Suzuki cross-coupling method. The resulting PET drug is purified first by semi-preparative high pressure liquid chromatography (HPLC), and then followed by solid-phase extraction to remove the HPLC buffer mixture. Finally, the PET drug is formulated in <10% ethanolic saline solution (USP) containing <1% sodium bicarbonate (USP), and the resulting PET drug product is then passed through a 0.22 micron sterile membrane filter for terminal sterilization and collected in a sterile pyrogen free collection vial to afford a formulated I.V. solution ready for dispensing and administration. ^{18}F-FDG: ^{18}F-FDG will be administered immediately upon arrival at the PET center, or at most within 12 hours from the time of the end of synthesis (EOS). Based on the drug label, ^{18}F-FDG can be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

7.2 Packaging and Labeling

The label on the bottles with CT1812 will contain the following information in the English language:

- Protocol number: COG0105
- Expiration date
- Lot number

- Contents
- Weight
- Storage conditions
- The sentence, “For Clinical Trial Use Only”
- Name of the Investigator
- Name, address and telephone number of the Sponsor

7.3 Administration

CT1812 or matching placebo will be administered once each morning as a 300 mg or 100 mg oral dose (2 capsules). Capsules will be swallowed with ~240 mL of water. In order to ensure appropriate specimen collection times relative to dosing; on clinic days, participants will be asked to take their medication at the clinic upon the instruction of the site staff.

7.3.1 Safety Stopping Rules

The occurrence of any one of the following events will result in suspension of administration of study drug in all participants until safety information can be further reviewed by the Sponsor and Medical Monitor.

- Two occurrences of the same or similar SAE assessed as probably or possibly related to dosing with investigational product
- Two or more different participants with the same or similar severe AE assessed as probably or possibly related to dosing with the investigational product
- Four or more participants with the same or similar moderate AE which is possibly or probably related to dosing with investigational product

Under these circumstances, the Sponsor and Medical Monitor will review the available safety data and, in consultation with the study principal investigator, recommend whether dosing should continue, or if study drug administration should be terminated or dose reduced, or if additional monitoring procedures or safety precautions need to be employed.

If a stopping rule is achieved, selective unblinding of the participants involved may be performed by the Sponsor to determine if the SAEs/AEs are isolated to a single dose group or if they occurred in placebo participants.

The study or a dose group may also be terminated if the Medical Monitor, Study Director and Sponsor, in consultation with the lead principal investigator, determine that any adverse event(s) are occurring that are intolerable or pose a medically unacceptable safety risk.

FOR INDIVIDUAL PARTICIPANTS:

Participants who develop a severe adverse event or laboratory abnormality will not receive any additional doses and will be monitored until resolution of the AE or the return of laboratory abnormality to the acceptable screening value(s). Study drug may be re-initiated after consultation with medical monitor and sponsor. Any participant with:

- elevated ALT or AST greater than 5 X ULN should have dosing with study drug stopped and have laboratory tests repeated every 3-4 days until levels return to less than or equal to 1.5 X ULN. If the medical monitor and investigator are in agreement, study drug may be continued while a confirmatory ALT/AST is obtained within 3 days. If the confirmatory ALT/AST tests are below 5 X ULN, study drug may be continued. The frequency of the laboratory tests may be modified after discussion with the medical monitor if the liver enzymes are in a decreasing trend.
- Elevated ALT or AST greater than 3 X ULN in combination with total bilirubin > 2 X ULN or INR > 1.5 X ULN OR an ALT or AST > 3 X ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) should have dosing with study drug stopped and have laboratory testing repeated every 3-4 days. If the medical monitor and investigator are in agreement, study drug may be continued while a confirmatory laboratory testing is obtained within 3 days. If these criteria are no longer met, study drug can be continued at the discretion of the medical monitor and investigator. The frequency of the laboratory tests may be modified after discussion with the medical monitor if the laboratory tests are trending towards normal.
- An increase in serum creatinine by 0.3 mg/dL (24.4 micromol/L) or 150% of baseline that is without clinical explanation of another etiology will result in repeated serum chemistry testing within 3-7 days. If the serum creatinine elevation is confirmed on repeated testing the study drug will be discontinued. If the serum creatinine elevation resolves upon

subsequent testing after study drug is discontinued the study drug may be restarted with serum creatinine monitoring at the discretion of the medical monitor and investigator.

- An increase in serum calcium to ≥10.5 mg/dL (2.63 mmol/L) that is without clinical explanation of another etiology will result in repeated serum chemistry testing within 3-7 days. If the serum calcium elevation is confirmed on repeated testing the study drug will be discontinued. If the serum calcium elevation resolves upon subsequent testing after study drug is discontinued the study drug may be restarted with serum calcium monitoring at the discretion of the medical monitor and investigator.
- Note: Fractional excretion of calcium will be monitored in each participant and interpreted in conjunction with serum creatinine and serum calcium. Given the ability of fractional excretion to fluctuate, no upper limit for discontinuing study drug based on fractional excretion of calcium has been set but it may be used as a stopping rule if persistent unexplained increases in fractional excretion of calcium are observed.

Note: Any unanticipated SAEs that are 'related' should be reported to the National Institute on Aging within 48 hours of knowledge of the same.

7.3.2 Accountability

The Investigator or their appointed designee is responsible for ensuring that deliveries of study drug are correctly dispensed and recorded, that the product is handled and stored safely and properly, and that it is only being given to participants in accordance with this protocol.

Sites will keep a current log of drug accountability recording:

- What drug supply was received from the Sponsor
- What drug supply was dispensed to each participant
- What drug supply is current in inventory
- What drug supply was destroyed or returned to the Sponsor for destruction

Note: Drug accountability is the responsibility of the Investigator; a written account will be required for all discrepancies.

The Sponsor's designated Monitor must verify all accountability records during periodic monitoring visits. Unused and used study drug must be stored on site until such accountability has taken place and authorization is received from the Sponsor or Sponsor's designee that the study drug may be returned or destroyed.

7.4 Overdose/Toxicity Management

No specific pharmacologic antagonist or antidote exists for CT1812. Therefore, overdose or clinical toxicity should be managed with supportive care and pharmacologic treatments directed at specific symptoms (i.e. benzodiazepines for agitation or antipyretics for fever).

7.5 Blinding and Randomization

This is a double-blind, placebo controlled study. Study drug will consist of either of two doses of CT1812 or placebo. The placebo will be identical in appearance to both doses of the active CT1812.

The non-blinded statistician assigned to the trial will generate a list with the appropriate number of 4 digit individual study IDs randomly for each arm, randomly assigned to either CT1812 300 mg, CT1812 100 mg or placebo treatment in a 1:1:1 ratio. Randomization will include stratification on the MMSE score with two strata of 18-22 and 23-26.

Should any participant withdraw from the study prior to study completion, leading to insufficient or uninformative data for analysis, the participant may be replaced, at the sponsor's discretion. This participant will be given the same treatment assignment (by the unblinded statistician) as the withdrawn participant.

8 INVESTIGATORS, SITES AND DURATION

8.1 Investigator and Site

This single-center trial will be conducted at [redacted]

8.2 Duration of Study

Each participant and caregiver will participate in a screening period of up to 60 days, followed by the primary double-blind treatment period of 24 weeks (169 days +/-2) followed by an optional double-blind extension treatment period of another 24 weeks (337 days +/-2). A follow up visit will occur 2 weeks after the last day of dosing. Including the screening period, the total duration of participant participation in the study is up to 36 week for the primary study or up to 60 weeks for the extension study. If a delay occurs with subjects progressing from the primary study to the extension study, a maximum of 4 weeks will be permitted.

8.3 Termination of Study

This study may be terminated at the discretion of the Sponsor. Occurrence of the stopping rules defined in Section 7.3.1 may result in early termination of the study.

9 STUDY POPULATION

9.1 Number of Participants

Up to 21 participants will be randomized. A maximum of 25 participants may receive study drugs and PET tracers, if replacement of drop-outs occurs.

9.2 Inclusion Criteria

Participants may be included in the study only if they meet all of the following criteria:

1) Men, and women of non-childbearing potential, 50-85 years of age inclusively, with a diagnosis of mild to moderate Alzheimer's disease according to the 2011 National Institute on Aging – Alzheimer's Association criteria (McKhann et al, 2011) and at least a 6 month decline in cognitive function documented in the medical record.
    a) Non-childbearing potential for women is defined as postmenopausal [last natural menses greater than 24 months; in women under age 55, menopausal status will be documented with serum follicle stimulating hormone (FSH) test] or undergone a documented bilateral tubal ligation or hysterectomy.
    b) Male participants who are sexually active with a woman of child-bearing potential must agree to use condoms during the trial and for 3 months after last dose unless the woman is using an acceptable means of birth control. Acceptable forms of birth control include abstinence, birth control pills, or any double combination of: intrauterine device (IUD), male or female condom, diaphragm, sponge, and cervical cap.
2) Neuroimaging (MRI) obtained during screening consistent with the clinical diagnosis of Alzheimer's disease and without findings of significant exclusionary abnormalities (see exclusion criteria, number 3).
3) MMSE 18-26 inclusive.
4) A positive amyloid (e.g., Pittsburgh imaging compound B) scan at screening, or history of a positive amyloid scan prior to study entry, or prior lumbar puncture with a CSF Aβ concentration consistent with Alzheimer's disease.

5) Formal education of eight or more years.

6) Must have a caregiver who sees them at least 10 hours per week, oversees the administration of study drug, and is willing and able to oversee administration of study medication and participate in all clinic visits and some study assessments. The caregiver must provide written informed consent to participate in the study.

7) Living at home or in the community (assisted living acceptable).

8) Able to swallow CT1812 capsules.

9) Stable pharmacological treatment of any other chronic conditions for at least 30 days prior to screening.

10) Capable of providing either written informed consent or oral assent to the study procedures and for use of protected health information (Health Insurance Portability and Accountability Act [HIPAA] Authorization, if applicable). If the Participant can provide only assent, their legally authorized representative also must provide written informed consent. Written informed consent also shall be obtained from the responsible caregiver. All consent processes must be undertaken in the presence of a witness and prior to any study procedures.

11) Must consent to apolipoprotein E (ApoE) genotyping.

12) Generally healthy with mobility (ambulatory or ambulatory-aided, i.e., walker or cane), vision and hearing (hearing aid permissible) sufficient for compliance with testing procedures.

13) Able to complete all screening evaluations.

9.3 Exclusion Criteria

Participants will be excluded from the study if any of the following conditions apply:

1) Hospitalization or change of chronic concomitant medication within one month prior to screening.

2) Patients living in a continuous care nursing facility.

3) Screening MRI of the brain indicative of significant abnormality, including, but not limited to, prior hemorrhage or infarct >1 cm^3, >3 lacunar infarcts, cerebral contusion, encephalomalacia, aneurysm, vascular malformation, subdural hematoma, hydrocephalus, space-occupying lesion (e.g. abscess or brain tumor such as meningioma).

4) MRI incompatible implants and other contraindications for MRI, such as pacemaker, artificial joints, non-removable body piercings, etc. Additionally, participants who meet the following imaging exclusion criteria will not be included in this study:

    a. Claustrophobia that will result in significant anxiety and difficulty lying still for brain imaging (MRI or PET).

    b. Participation in other research studies involving ionizing radiation within one year of the PET scans that would cause the participant to exceed the yearly dose limits for healthy volunteers.

    c. History of IV drug use that would prevent venous access for PET tracer injection.

    d. Severe motor problems that prevent the participant from lying still for brain imaging.

    e. Severe chronic pain (e.g., as the result of rheumatoid arthritis) that would prevent them from lying still during brain imaging.

5) Clinical or laboratory findings consistent with:

    a) Other primary degenerative dementia, (dementia with Lewy bodies, fronto-temporal dementia, Huntington's disease, Jacob-Creutzfeld Disease, Down's syndrome, etc.).

    b) Other neurodegenerative condition (Parkinson's disease, amyotrophic lateral sclerosis, etc.)

    c) Seizure disorder

    d) Other infectious, metabolic or systemic diseases affecting the central nervous system (syphilis, present hypothyroidism, present vitamin B12 or folate deficiency, other laboratory values) etc.)

6) A current Diagnostic and Statistical Manual of Mental Disorders-V (DSM-V) diagnosis of active major depression, schizophrenia or bipolar disorder. Patients with depressive symptoms successfully managed by a stable dose of an antidepressant are allowed entry.

7) Clinically significant, advanced or unstable disease that may interfere with outcome evaluations, such as:

    a) Chronic liver disease, liver function test abnormalities or other signs of hepatic insufficiency (ALT, AST, total bilirubin > 1.5 x ULN)

    b) Respiratory insufficiency

c) Renal insufficiency defined as eGFR <45 mL/min based on the CKD-EPI formula, [redacted]

d) Heart disease (myocardial infarction, unstable angina, heart failure, cardiomyopathy within six months before screening)

e) Bradycardia (<45/min.) or tachycardia (>100/min.)

f) Poorly managed hypertension (systolic >160 mm Hg and/or diastolic >95 mm Hg) or hypotension (systolic <90 mm Hg and/or diastolic <60 mm Hg)

g) Uncontrolled diabetes defined by glycosylated hemoglobin (HbA1c) >7.5%

8) History of cancer within 3 years of screening with the exception of fully excised non-melanoma skin cancers or non-metastatic prostate cancer that has been stable for at least 6 months.

9) Seropositive for human immunodeficiency virus (HIV).

10) History of acute/chronic hepatitis B or C and/or carriers of hepatitis B (seropositive for Hepatitis B surface antigen [HbsAg] or anti-Hepatitis C [HCV] antibody).

11) Clinically significant abnormalities in screening laboratory tests, including:

a) hematocrit less than 33% for males and less than 30% for females

b) absolute neutrophil cell count of 1200/uL (with the exception of a documented history of a chronic benign neutropenia), or platelet cell count of <120,000/uL

c) INR >1.4 or other coagulopathy, confirmed by repeat.

12) Disability that may prevent the patient from completing all study requirements (e.g. blindness, deafness, severe language difficulty, etc.).

13) Women who are fertile and of childbearing potential.

14) Within 4 weeks of screening visit or during the course of the study, concurrent treatment with antipsychotic agents (except risperidone ≤1.5 mg/day, quetiapine ≤100 mg/day, olanzapine ≤5 mg/day, and aripiprazole ≤10 mg/day), antiepileptics (except lamotrigine, gabapentin and pregabalin for nonseizure indications), centrally active anti-hypertensive drugs (e.g., clonidine, l-methyl dopa, guanidine, guanfacine, etc.), opiate analgesics, systemic corticosteroids, psychostimulants, antiparkinsonian medications (except for non-parkinsonian indications) and mood stabilizers (e.g., valproate, lithium), sedatives and anxiolytics with the exception that use of short- to medium-acting benzodiazepines for treatment of insomnia is permitted,

however, use of sedatives or hypnotics should be avoided for 8 hours before administration of cognitive tests. See Appendix A and B for a representative list.

15) Any disorder that could interfere with the absorption, distribution, metabolism or excretion of drugs (e.g. small bowel disease, Crohn's disease, celiac disease, or liver disease).

16) Nootropic drugs except stable AD meds (acetylcholinesterase inhibitors and memantine.

17) Suspected or known drug or alcohol abuse, i.e. more than approximately 60 g alcohol (approximately 1 liter of beer or 0.5 liter of wine) per day indicated by elevated MCV significantly above normal value at screening.

18) Suspected or known allergy to any components of the study treatments.

19) Enrollment in another investigational study or intake of investigational drug within the previous 30 days or five half lives of the investigational drug, whichever is longer.

20) Previous exposure to anti Aβ vaccines.

21) Exposure to passive immunotherapies for AD (e.g. monoclonal antibodies) within the previous 180 days to dosing, and BACE inhibitors within the previous 30 days to dosing.

22) Contraindication to undergoing an LP including, but not limited to: inability to tolerate an appropriately flexed position for the time necessary to perform an LP; INR > 1.4 or other coagulopathy; platelet count of < 120,000/μL; infection at the desired lumbar puncture site; taking anti-coagulant medication within 90 days of screening (Note: low dose aspirin is permitted); degenerative arthritis of the lumbar spine; suspected non-communicating hydrocephalus or intracranial mass; prior history of spinal mass or trauma.

23) Use of NSAIDs more than 2 days in within any 7 day period. Each incidence of use must be recorded in the source and Case Report Form (CRF).

24) Any condition, which in the opinion of the investigator or the sponsor makes the patient unsuitable for inclusion.

25) Intake of drugs or substances potentially involved in clinically significant CYP3A4 inhibition or induction or P-gp mediated drug interactions with CT1812, within 4 weeks or five half-lives of the interacting drug prior to administration of CT1812 and throughout the course of the study. Grapefruit juice should be avoided in the two weeks prior to dosing. See Appendix A and B for a list of these prohibited substances.

9.4 Withdrawal of Participants

A participant should be withdrawn from the study if any of the following occur:

1) Withdrawal of participant consent.

2) Investigator determines that withdrawal from the study is in the best interest of the participant.

3) Major protocol violation (i.e., circumstances where confounding conditions make it impossible to derive sound scientific or medical conclusions from the primary endpoint data generated on a participant).

4) Any condition, injury, or disease that becomes apparent during the study and necessitates the termination of the participant from the study; including events detailed in Section 7.3.1 - Safety Stopping Rules.

5) Administrative reason (e.g., termination of the clinical study by a Regulatory Agency or the Sponsor).

9.5 Participant Withdrawal Procedures

9.5.1 Follow-up Procedures for Participants Who Withdraw Prematurely

The date and the reason for study drug discontinuation or participant withdrawal from the study must be recorded on the Case Report Form. Participants who prematurely discontinue the study for any reason will be asked to attend the final/ early discontinuation visit but are not required to attend a follow up visit unless deemed necessary at the discretion of the investigator.

9.6 Procedures for Replacing Participants Who Withdraw

Should any participant withdraw from the study prior to study completion, leading to insufficient or uninformative data for analysis, the participant may be replaced, at the sponsor’s discretion If a participant is replaced, instructions in Section 7.5 will be followed for randomization and assignment of a study number.

10 TREATMENT PLAN AND METHODS

10.1 Schedules of Assessments – Primary and Extension

Table 1 - Schedule of Assessments – Primary Study Only

Visit Name and Number	V1				Baseline V2	V3	Blood draw only	V4	V5	V6	V7	V8	V9	V10	Final/ Early Discont-inuation V11	V12
Study Day	-60 to -1				1	15 (+/-2)	21 (+/-1)	29 (+/-2)	43 (+/-2)	64 (+/-2)	85 (+/-7)	106 (+/-2)	127 (+/-2)	148 (+/-2)	169 (+/-7)	183 (14 D (+/-2) from V11)
	Step 1	Step 2	Step 3	Step 4												
Informed consent capability	x															
Written informed consent [1]	x															
Demographic information	x															
General medical, surgical and psychiatric history	x															
Inclusion/exclusion criteria	x	x	x													
Modified Hachinski	x															
Geriatric Depression Score	x															
C-SSRS	x				x	x		x	x	x	x	x	x	x	x	
Diagnosis of Probable AD [2]	x															
^{18}F-FDG Imaging				x											x	
^{11}C -UCB-J Imaging (SV2A imaging)				x							x				x	
Amyloid imaging (e.g. ^{11}C -PiB Imaging)[3]			x													
MR Imaging (Safety MRI, resting state BOLD)		x									x				x	
MMSE	x								x		x		x		x	
ADAS-Cog 14, NTB [4]					x				x		x		x		x	
CDR-SB [5]					x				x		x		x		x	

Visit Name and Number	V1				Baseline V2	V3	Blood draw only	V4	V5	V6	V7	V8	V9	V10	Final/ Early Discont-inuation V11	V12
Study Day	-60 to -1				1	15 (+/-2)	21 (+/-1)	29 (+/-2)	43 (+/-2)	64 (+/-2)	85 (+/-7)	106 (+/-2)	127 (+/-2)	148 (+/-2)	169 (+/-7)	183 (14 D (+/-2) from V11)
	Step 1	Step 2	Step 3	Step 4												
ADCS-CGIC [5]					x				x		x		x		x	
ADCS-ADL [5]					x				x		x		x		x	
Physical Examination	x				x	x		x	x	x	x	x	x	x	x	x
ECG	x				x			x			x	x			x	x
Vital signs, weight [6, 10]	x				x	x		x	x	x	x	x	x	x	x	x
Hematology, biochemistry	x				x	x	x	x	x	x	x	x	x	x	x	x
Urinalysis	x				x	x		x	x	x	x	x	x	x	x	x
Coagulation [7]	x													x		
Serology: Syphilis, HIV, HepB, HepC [8]	x															
Thyroid panel (T3, T4, TSH), B12, folate [9]	x															
APOE status	x															
CSF sampling for PK and PD [12]				x											x	
Plasma sampling for PK [13]					x	x		x	x	x	x	x	x	x	x	
Dispense study drug [14]					x						x					
Drug return and drug accountability						x		x	x	x	x	x	x	x	x	
Recording concomitant medication	x				x	x		x	x	x	x	x	x	x	x	
Recording of adverse events [11]		x	x	x	x	x		x	x	x	x	x	x	x	x	

Key for Schedule of Assessments

1. Informed consent must be obtained prior to the participant undergoing any study-specific procedures.
2. Confirm AD diagnosis (NIA-AA 2011 criteria, McKhann et al, 2011]).
3. Perform brain amyloid imaging (PET scan). Amyloid imaging of the brain may not be required if there is evidence of positive Alzheimer's disease biomarkers based on amyloid PET imaging or CSF Aβ.
4. Cognitive testing will include the ADAS-Cog 14 and NTB. Cognitive assessments will be locally administered by trained site staff and then centrally scored by a qualified central reviewer. Sites will be provided with copies of the scored assessments for their own records.
5. Functional testing will include CDR-SB, ADCS-CGIC and ADCS-ADL
6. Vital signs will include body temperature, seated systolic and diastolic BP, pulse rate and respiratory rate (Section 15.1.5).
7. Coagulation panel may be repeated upon admission as medically indicated or required by local practice.
8. Serology for hepatitis B (HbsAg), hepatitis C (HCV) and HIV (Section 14.2).
9. Clinical laboratory testing (Section 14).
10. Height will be recorded only at screening; Weight will be collected at every visit. (Section 15.1.3).
11. During Screening (post-consent), only SAEs related to a study-specific procedure will be collected. For all related AEs of moderate or severe intensity ongoing at the end of the study, follow-up will continue until the event has resolved to baseline severity, the event is assessed as stable by the Investigator, or the patient is lost to follow-up or the patient withdraws consent.
12. CSF Sampling: (see Section 11).
13. Blood collection (see Section 14).
14. On clinic visit dates, subject should hold dose in AM and dosing should occur in the clinic.

Table 2 - Schedule of Assessments –Primary and Extension Study

Visit Name and Number	V1				Baseline V2	V3	Blood draw only	V4	V5	V6	V7	V8	V9	V10	V11	V12 E	V13	V14	Final / Early Discon t-inuatio n V15	V16
Study Day	**-60 to -1**				**1**	**15 (+/-2)**	**21 (+/-1)**	**29 (+/-2)**	**43 (+/-2)**	**64 (+/-2)**	**85 (+/-7)**	**106 (+/-2)**	**127 (+/-2)**	**148 (+/-2)**	**169 (+/-7)**	**211 (±3)**	**253 (±3)**	**295 (±3)**	**337 (+/-7)**	**351 (14 D (+/-2) from V15)**
	Step 1	Step 2	Step 3	Step 4																
Informed consent capability	x																			
Written informed consent [1]	x																			
Demographic information	x																			
General medical, surgical and psychiatric history	x																			
Inclusion/exclusion criteria	x	x	x																	
Modified Hachinski	x																			
Geriatric Depression Score	x																			
C-SSRS	x				x	x		x	x	x	x	x	x	x	x		x		x	
Diagnosis of Probable AD [2]	x																			
^{18}F-FDG Imaging				x											x				x	
^{11}C -UCB-J Imaging (SV2A imaging)				x							x				x				x	
Amyloid imaging (e.g. ^{11}C -PiB Imaging)[3]			x																	
MR Imaging (Safety MRI, resting state BOLD)		x									x				x				x	
MMSE	x								x		x		x		x		x		x	
ADAS-Cog 14, NTB [4]					x				x		x		x		x		x		x	

Visit Name and Number	**V1**				**Baseline V2**	**V3**	**Blood draw only**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12 E**	**V13**	**V14**	**Final / Early Discon t-inuatio n V15**	**V16**
Study Day	**-60 to -1**				**1**	**15 (+/-2)**	**21 (+/-1)**	**29 (+/-2)**	**43 (+/-2)**	**64 (+/-2)**	**85 (+/-7)**	**106 (+/-2)**	**127 (+/-2)**	**148 (+/-2)**	**169 (+/-7)**	**211 (±3)**	**253 (±3)**	**295 (±3)**	**337 (+/-7)**	**351 (14 D (+/-2) from V15)**
	Step 1	Step 2	Step 3	Step 4																
CDR-SB [5]					x				x		x		x		x		x		x	
ADCS-CGIC [5]					x				x		x		x		x		x		x	
ADCS-ADL [5]					x				x		x		x		x		x		x	
Physical Examination	x				x	x		x	x	x	x	x	x	x	x	x	x	X	x	x
ECG	x				x			x			x	x			x		x		x	x
Vital signs, weight [6, 10]	x				x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
Hematology, biochemistry	x				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Urinalysis	x				x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
Coagulation [7]	x													x						
Serology: Syphilis, HIV, HepB, HepC [8]	x																			
Thyroid panel (T3, T4, TSH), B12, folate [9]	x																			
APOE status	x																			
CSF sampling for PK and PD [12]				x											x				x	
Plasma sampling for PK [13]					x	x		x	x	x	x	x	x	x			x		x	
Dispense study drug [14]					x						x				x		x			
Drug return and drug accountability						x		x	x	x	x	x	x	x	x	x	x	x	x	
Recording concomitant medication	x				x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
Recording of adverse events [11]		x	x	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x

Key for Schedule of Assessments

1. Informed consent must be obtained prior to the participant undergoing any study-specific procedures.
2. Confirm AD diagnosis (NIA-AA 2011 criteria, McKhann et al, 2011]).
3. Perform brain amyloid imaging (PET scan). Amyloid imaging of the brain may not be required if there is evidence of positive Alzheimer's disease biomarkers based on amyloid PET imaging or CSF Aβ.
4. Cognitive testing will include the ADAS-Cog 14 and NTB. Cognitive assessments will be locally administered by trained site staff and then centrally scored by a qualified central reviewer. Sites will be provided with copies of the scored assessments for their own records.
5. Functional testing will include CDR-SB, ADCS-CGIC and ADCS-ADL
6. Vital signs will include body temperature, seated systolic and diastolic BP, pulse rate and respiratory rate (Section 15.1.5).
7. Coagulation panel may be repeated upon admission as medically indicated or required by local practice.
8. Serology for hepatitis B (HbsAg), hepatitis C (HCV) and HIV (Section 14.2).
9. Clinical laboratory testing (Section 14).
10. Height will be recorded only at screening. Weight will be collected at every visit. (Section 15.1.3).
11. During Screening (post-consent), only SAEs related to a study-specific procedure will be collected. For all related AEs of moderate or severe intensity ongoing at the end of the study, follow-up will continue until the event has resolved to baseline severity, the event is assessed as stable by the Investigator, or the patient is lost to follow-up or the patient withdraws consent.
12. CSF Sampling: (see Section 11).
13. Blood collection (see Section 14).
14. On clinic visit dates, subject should hold dose in AM and dosing should occur in the clinic.
15. The Visit 15 lumbar puncture and collection of CSF samples for PK and PD analyses is optional.

10.2 Study Specific Procedures

10.2.1 Screening Visit 1, Steps 1-4

Screening assessments may be performed during multiple visits over a period of 60 days prior to dosing with the determination of inclusion and exclusion criteria occurring over Visits V1 through V1.3. If needed for biomarker collection or interpretation or for logistical reasons, this period can be prolonged with written approval from the Sponsor. Steps 3 and 4 assessments may only be performed after completion of Steps 1 and 2 assessments which are necessary for determination of eligibility for continued participation. The order of individual assessments within a step is not fixed, unless indicated otherwise. Different screening assessments associated with each step may be performed on a single visit day or spread over multiple visits days. Eligible participants based on Steps 1 to 4 assessments will return to the site to have Baseline/ Visit 2. Although visit numbers are specified, fewer or additional visits can occur based on the above, and the numbering is considered guidance.

The following procedures will be performed as part of the Step 1/ Screening visit/s:

- Determine informed consent capability
- Obtain signed Informed Consent Form from participant
- Evaluate participant eligibility against study inclusion/exclusion criteria including administration of the Mini-Mental State Exam (MMSE), Geriatric Depression Scale (GDS) and modified Hachinski scale. (See section 16 for details)
- Record demographic information and confirm ethnicity
- Perform complete physical examination (see Section 15.1.3 for details)
- Medical, surgical and psychiatric history (see Section 15.1.4 for details)
- Measure and record vital signs and weight (see Section 15.1.5 for details)
- Confirm diagnosis of Probable AD according to 2011 NIA-AA criteria
- Perform 12-lead ECG (see Section 15.1.6 for details)
- Draw blood and prepare samples for ApoE status. Apolipoprotein E (ApoE) genotype is associated with the risk and age of onset of AD. Blood samples (approximately 10 mL) to perform this testing will be collected and will be utilized to further understanding of response to CT1812. The genotyping is mandatory for participation in the study

and the results will not be revealed to either the participant or caregiver or study partner.

- Draw blood and prepare samples for serum chemistry, hematology, viral serology, thyroid panel and coagulation panel (see Section 14 for details). Abnormal results at screening will exclude a participant unless the investigator is aware of a specific reason that can explain the abnormality (e.g., elevated creatine phosphokinase [CPK] 24 hours after strenuous exercise). Should an abnormal lab remain abnormal on repeat the participant will be excluded.
- Collect urine sample for urinalysis (see Section 14.1 for details)
- Record concomitant medications
- Administer C-SSRS (see Section 16.1 for details)

The following procedures will be performed as part of the Step 2/ Screening visit/s:

- Perform brain MRI
- Record any SAEs that have occurred since the Screening Visit

The following procedures will be performed as part of the Step 3/ Screening visit/s:

- Perform brain amyloid imaging of the brain (e.g., C-PiB Imaging). Amyloid imaging may not be required if there is biomarker evidence of Alzheimer's disease based on prior amyloid PET imaging or CSF Aβ
- Record any SAEs that have occurred since the Screening Visit

The following procedures will be performed as part of the Step 4/ Screening visit/s:

- Perform ^{11}C-UCB-J Imaging
- Perform ^{18}F-FDG Imaging
- Perform a lumbar puncture and collect CSF samples for PK and PD analyses
- After participant has met all inclusion requirements up through step 4 of screening, the pharmacy should obtain the participant randomization assignment for study subject; ideally no less than one week before participant returns for baseline visit.
- Record any SAEs that have occurred since the last visit.

10.2.2 Visit 2, Study Day 1 – Baseline

Baseline Visit

(Week 0) The baseline visit may only be initiated following completion of all Screening assessments and required approvals. The Baseline visit procedures may be completed over multiple days and will typically require at least two (2) visits. All baseline procedures, including randomization must be completed within 60 days of initiation of Screening Visit procedures.

Following completion of all baseline procedures and confirmation that the baseline ^{18}F-FDG PET has passed central quality control, participants who continue to meet all protocol inclusion criteria and no exclusion criteria, will be randomized and dispensed study medication. The following will be conducted as part of the baseline visit activities:

- Perform cognitive testing and functional assessments (see Section 16)
- Perform interval history
- Administer C-SSRS (see Section 16.1 for details)
- Perform physical examination (see Section 15.1.3 for details)
- Measure and record vital signs and weight (see Section 15.1.5 for details)
- Perform 12-lead ECG (see Section 15.1.6 for details)
- Draw blood and prepare sample for serum chemistry and hematology (see Section 14.1 for details)
- Collect urine sample for urinalysis (see Section 14.1 for details)
- Draw blood and prepare samples for PK
- Record concomitant medications
- Record any SAEs that have occurred since the Screening Visit
- Administer first dose of study drug
- Dispense double-blind study drug as required up to day 85+/- 7
- Schedule participant to return for Visit 3 in 2 weeks.

10.2.3 Visit 3, Study Day 15

The following procedures will be conducted on Day 15 (±2 days):

- Administer C-SSRS (see Section 16.1 for details)
- Perform physical examination (see Section 15.1.3 for details)
- Measure and record vital signs and weight (see Section 15.1.5 for details)
- Draw blood and prepare sample for serum chemistry and hematology (see Section 14.1 for details)
- Collect urine sample for urinalysis (see Section 14.1 for details)
- Draw blood and prepare samples for PK
- Record concomitant medications
- Record AEs
- Administer study drug for that day
- Perform study drug accountability
- Schedule participant to return for Visit 4 in 2 weeks.

10.2.4 Blood Draw, Study Day 21

The following procedure conducted on Day 21 (±1 days):

- Draw blood and prepare sample for serum chemistry and hematology (see Section 14.1 for details)

10.2.5 Visit 4, Study Day 29

The following procedures will be conducted on Day 29 (±2 days):

- Administer C-SSRS (see Section 16.1 for details)
- Perform physical examination (see Section 15.1.3 for details)
- Measure and record vital signs and weight (see Section 15.1.5 for details)
- Perform 12-lead ECG (see Section 15.1.6 for details)
- Draw blood and prepare sample for serum chemistry and hematology (see Section 14.1 for details)

- Collect urine sample for urinalysis (see Section 14.1 for details)
- Draw blood and prepare samples for PK
- Record concomitant medications
- Record AEs
- Administer study drug for that day
- Perform study drug accountability
- Schedule participant to return for Visit 5 in 2 weeks.

10.2.6 Visit 5, Study Day 43

The following procedures will be conducted on Day 43 (±2 days):

- Perform MMSE
- Perform cognitive testing and functional assessments (see Section 14)
- Administer C-SSRS (see Section 16.1 for details)
- Perform physical examination (see Section 15.1.3 for details)
- Measure and record vital signs and weight (see Section 15.1.5 for details)
- Draw blood and prepare sample for serum chemistry and hematology (see Section 14.1 for details)
- Collect urine sample for urinalysis (see Section 14.1 for details)
- Draw blood and prepare samples for PK
- Record concomitant medications
- Record AEs
- Administer study drug for that day
- Perform study drug accountability
- Schedule participant to return for Visit 6 in 3 weeks.

10.2.7 Visit 6, Study Day 64

The following procedures will be conducted on Day 64 (±2 days):

- Administer C-SSRS (see Section 16.1 for details)
- Perform physical examination (see Section 15.1.3 for details)
- Measure and record vital signs and weight (see Section 15.1.5 for details)
- Draw blood and prepare sample for serum chemistry and hematology (see Section 14.1 for details)
- Collect urine sample for urinalysis (see Section 14.1 for details) Draw blood and prepare samples for PK
- Record concomitant medications
- Record AEs
- Administer study drug for that day
- Perform study drug accountability
- Schedule participant to return for Visit 7 in 3 weeks.

10.2.8 Visit 7, Study Day 85

The following procedures will be conducted on Day 85 (±7 days):

- Perform MMSE
- Perform cognitive testing and functional assessments (see Section 16)
- Administer C-SSRS (see Section 16.1 for details)
- Perform brain MRI
- Perform ^{11}C-UCB-J Imaging
- Perform physical examination (see Section 15.1.3 for details)
- Measure and record vital signs and weight (see Section 15.1.5 for details)
- Perform 12-lead ECG (see Section 15.1.6 for details)
- Draw blood and prepare sample for serum chemistry and hematology (see Section 14.1 for details)

- Collect urine sample for urinalysis (see Section 14.1 for details)
- Draw blood and prepare samples for PK
- Record concomitant medications
- Record AEs
- Administer study drug for that day
- Perform study drug accountability
- Dispense study drug for remainder of study
- Schedule participant to return for Visit 8 in 3 weeks

10.2.9 Visit 8, Study Day 106 (±2 days):

The following procedures will be conducted on Day 106:

- Administer C-SSRS (see Section 16.1 for details)
- Perform physical examination (see Section 15.1.3 for details)
- Measure and record vital signs and weight (see Section 15.1.5 for details)
- Perform 12-lead ECG (see Section 15.1.6 for details)
- Draw blood and prepare sample for serum chemistry and hematology (see Section 14.1 for details)
- Collect urine sample for urinalysis (see Section 14.1 for details)
- Draw blood and prepare samples for PK
- Record concomitant medications
- Record AEs
- Administer study drug for that day
- Perform study drug accountability
- Schedule participant to return for Visit 9 in 3 weeks.

10.2.10 Visit 9, Study Day 127 (±2 days):

The following procedures will be conducted on Day 127:

- Perform MMSE
- Perform cognitive testing and functional assessments (see Section 16)
- Administer C-SSRS (see Section 16.1 for details)
- Perform physical examination (see Section 15.1.3 for details)
- Measure and record vital signs and weight (see Section 15.1.5 for details)
- Draw blood and prepare sample for serum chemistry and hematology (see Section 14.1 for details)
- Collect urine sample for urinalysis (see Section 14.1 for details)
- Draw blood and prepare samples for PK
- Record concomitant medications
- Record AEs
- Perform study drug accountability
- Schedule participant to return for Visit 10 in 2 weeks.

10.2.11 Visit 10, Study Day 148 (±2 days):

The following procedures will be conducted on Day 148:

- Administer C-SSRS (see Section 16.1 for details)
- Perform physical examination (see Section 15.1.3 for details)
- Measure and record vital signs and weight (see Section 15.1.5 for details)
- Draw blood and prepare sample for serum chemistry, hematology and coagulation panel (see Section 14.1 for details)
- Collect urine sample for urinalysis (see Section 14.1 for details)
- Draw blood and prepare samples for PK
- Record concomitant medications
- Record AEs

- Administer study drug for that day
- Perform study drug accountability
- Schedule participant to return for Visit 11 in 3 weeks.

10.2.12 Visit 11, Study Day 169 (For Primary Study only: End of Treatment / Early Discontinuation)

For subjects participating in the Primary Study only **and not participating in the Extension Study**, this visit will serve as the end of treatment visit.

The following procedures will be conducted on Day 169: (±7 days):

- Perform MMSE
- Perform cognitive testing and functional assessments (see Section 16)
- Administer C-SSRS (see Section 16.1 for details)
- Perform physical examination (see Section 15.1.3 for details)
- Measure and record vital signs and weight (see Section 15.1.5 for details)
- Perform 12-lead ECG (see Section 15.1.6 for details)
- Draw blood and prepare sample for serum chemistry and hematology (see Section 14.1 for details) as well as for coagulation testing (prothrombin time [PT/INR]).
- Collect urine sample for urinalysis (see Section 14.1 for details)
- Draw blood and prepare samples for PK
- Perform ^{11}C-UCB-J Imaging
- Perform ^{18}F-FDG Imaging
- Perform MRI Imaging
- Perform a lumbar puncture and collect CSF samples for PK and PD analyses
- Record concomitant medications
- Record any SAEs that have occurred since the last visit
- Administer dose of study drug
- Perform study drug accountability

10.2.13 Primary Study - Visit 12, Day 183 (14 days (+/-2)

- Physical examination
- ECG
- Vital signs, weight
- Hematology, biochemistry
- Urinalysis

10.2.14 Extension Study - Visit 12E, Day 211 (+/-3)

- Perform physical examination (see Section 15.1.3 for details)
- Measure and record vital signs and weight (see Section 15.1.5 for details)
- Draw blood and prepare sample for serum chemistry and hematology
- Collect urine sample for urinalysis (see Section 14.1 for details)
- Record concomitant medications
- Record any SAEs that have occurred since the last visit
- Perform study drug accountability

10.2.15 Extension Study - Visit 13, Day 253 (+/-3)

- Perform MMSE
- Perform cognitive testing and functional assessments (see Section 16)
- Administer C-SSRS (see Section 16.1 for details)
- Perform physical examination (see Section 15.1.3 for details)
- Measure and record vital signs and weight (see Section 15.1.5 for details)
- Perform 12-lead ECG (see Section 15.1.6 for details)
- Draw blood and prepare sample for serum chemistry and hematology
- Collect urine sample for urinalysis (see Section 14.1 for details)
- Draw blood and prepare samples for PK
- Record concomitant medications
- Record any SAEs that have occurred since the last visit

- Administer final dose of study drug
- Perform study drug accountability

10.2.16 Extension Study - Visit 14, Day 295 (+/-3) -

- Perform physical examination (see Section 15.1.3 for details)
- Measure and record vital signs and weight (see Section 15.1.5 for details)
- Draw blood and prepare sample for serum chemistry and hematology
- Collect urine sample for urinalysis (see Section 14.1 for details)
- Record concomitant medications
- Record any SAEs that have occurred since the last visit
- Perform study drug accountability

10.2.17 Extension Study - Visit 15, Study Day 337 / End of Treatment / Early Discontinuation

The following procedures will be conducted on Day 337: (±7 days):

- Perform MMSE
- Perform cognitive testing and functional assessments (see Section 16)
- Administer C-SSRS (see Section 16.1 for details)
- Perform physical examination (see Section 15.1.3 for details)
- Measure and record vital signs and weight (see Section 15.1.5 for details)
- Perform 12-lead ECG (see Section 15.1.6 for details)
- Draw blood and prepare sample for serum chemistry and hematology (see Section 14.1 for details) as well as for coagulation testing (prothrombin time [PT/INR]).
- Collect urine sample for urinalysis (see Section 14.1 for details)
- Draw blood and prepare samples for PK
- Perform ^{11}C-UCB-J Imaging
- Perform ^{18}F-FDG Imaging
- Perform MRI Imaging

- Optional - Perform a lumbar puncture and collect CSF samples for PK and PD analyses
- Record concomitant medications
- Record any SAEs that have occurred since the last visit
- Administer final dose of study drug
- Perform study drug accountability

10.2.18 Extension Study - Visit 16 / Day 352

- Physical examination
- ECG
- Vital signs, weight
- Hematology, biochemistry
- Urinalysis

10.3 Concomitant Medications and Other Restrictions

All medications mentioned in the exclusion criteria (Section 9.3) are expressly prohibited at any time during the study. Exceptions to the list of excluded medications may be made on a case-by-case basis if discussed and approved by the medical monitor in advance. Intake of drugs or substances potentially involved in clinically significant CYP3A4 or P-gp mediated drug interactions with CT1812, within 4 weeks or five half-lives of the interacting drug prior to administration of CT1812 and throughout the course of the study. Grapefruit juice should be avoided in the two weeks prior to dosing. See Appendix A for a list of these prohibited substances.

Participants may be on stable doses (at least 30 days prior to screening) of an acetylcholinesterase inhibitor and/or memantine and continue these medications during the study. Participants may be on a stable dose (at least 60 days prior to screening) of a selective serotonin reuptake inhibitor antidepressant and may continue this medication during the study.

11 CSF COLLECTION ASSESSMENTS

11.1 Lumbar Puncture

Each participant will undergo a lumbar puncture as part of the screening process and with the Day 169 visit. Lumbar punctures will be performed by study physicians specifically trained in the

procedure. Prior to the LP, a coagulation panel will be obtained to rule out a clotting disorder. Participants will be excluded from having an LP if he or she has an allergy to all local anesthetics (such as lidocaine) and/or has any medical condition requiring treatment with warfarin or heparin. The investigator may choose to have the lumbar puncture performed with the help of fluoroscopy. Lumbar punctures performed with the help of x-rays will be done at Yale-New Haven Hospital. Obtained CSF should be sent for cell counts (white blood cells and red blood cells, with differential if either of the counts is abnormal), CSF protein, and CSF glucose.

Approximately 15 mL of CSF will be collected at each lumbar puncture.

11.2 Timing of CSF Collections

At baseline and Day 169, CSF will be collected prior to the administration of the study drug dose due on that study day.

11.3 Volume of CSF Collected

The total volume of CSF collected from each participant during this study will be approximately 30 mL.

11.4 Handling, Shipping, Storage and Analysis of CSF

Refer to the Laboratory Procedures Manual for the handling of CSF samples. Participant CSF specimens collected during this study may be stored for up to 15 years and used to further the knowledge of CT1812.

12 PET IMAGING

Participants will have two ^{18}F-FDG, three ^{11}C-UCB-J scans, and one ^{11}C-PiB scan as part of their research participation.

PET scans are acquired as participants lie supine on the scanner bed. Venous catheters will be used for intravenous administration of the radiotracer PET scans will be performed with the Siemens HRRT. An attenuation correction scan is obtained immediately before or after each emission scan. For each PET scan with ^{11}C-UCB-J, up to 20 mCi will be administered by infusion pump, followed by dynamic PET data acquisition. Maximum mass dose from the radioligand will be limited to ≤3.25 µg to minimize any self-occupancy. For ^{11}C-PiB, the maximum dose is 15 mCi and for ^{18}F-FDG, the maximum dose is 5 mCi of ^{18}F-FDG. For each of these, the scan extends

for up to 90 min. Vital signs (blood pressure, pulse and respiration) are collected prior to and during each PET scan. The participants will have fasted for at least 4 h prior to the ^{18}F-FDG scan.

Participants with history of prior radiation exposure for research purposes or exposure to workplace radiation within the past year such that participation in this study would place them over the FDA limits for annual radiation exposure will be excluded from participating in this study. If a positive result is received, study participation will be cancelled.

13 MAGNETIC RESONANCE IMAGING (MRI)

Participants will have a brain MRI scan as part of the screening evaluation. MRI scans will take place at [redacted]. Participants that have any contraindications for MRI studies, including claustrophobia, the presence of metal (ferromagnetic) implants, or cardiac pacemaker will be excluded from participating in this the study.

The MRI will be performed using either [redacted]. The MRI will ensure that patients do not meet exclusion criteria by showing evidence of infection, infarction, or other focal brain lesions. Participants with multiple lacunes, or lacunes in a critical memory structure, will also be excluded. The MRI will take approximately 30 minutes to complete. We will not use sedation or MRI with contrast.

Every time an MRI is acquired, the following MRI acquisition sequence will be acquired using a [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

14 BLOOD AND URINE COLLECTION

14.1 Clinical Laboratory Testing

Hematology testing will include red blood cell count, erythrocyte mean corpuscular hemoglobin concentration (MCHC), erythrocyte mean corpuscular volume (MCV), hematocrit, hemoglobin, leukocyte count, and absolute counts of monocytes, neutrophils, basophils, eosinophils and platelets.

Serum chemistry analyses will include glucose, calcium, albumin, total protein, sodium, potassium, bicarbonate, chloride, magnesium, BUN, creatinine, creatine kinase, alkaline phosphatase, ALT, AST, bilirubin, lipase, lactate dehydrogenase (LDH) and phosphorus.

Urinalysis will include osmolality, creatinine, calcium, sodium, turbidity, color, specific gravity, pH, protein, glucose, ketones, bilirubin, blood, urobilinogen, nitrite, leukocytes, and microscopic particles. Urine should not be first morning void. Microscopic examination will be performed if urinalysis results are abnormal for bacteria, casts, epithelial cells, erythrocytes or leukocytes. Urine should be collected within two hours of blood draws for hematology and chemistry panels. Should not be first morning urine. Trace protein will be considered positive.

14.2 Screening Laboratory Tests

The following will be performed only at screening to confirm participant eligibility:

- Viral serology: hepatitis B antigen, anti-hepatitis C antibody and anti-HIV antibodies.
- Coagulation testing (prothrombin time [PT/INR]). Coagulation testing may be repeated if medically indicated or if required by local practice.
- Thyroid panel, B12 and folate

14.3 Blood Sample collection of Pharmacokinetic and Pharmacodynamic Analyses

14.3.1 Timing of Blood Sample Collection

- On clinic visit days, blood samples for the measurement of plasma CT1812 levels and proteomics will be drawn prior to administration of study drug due for that day.

14.4 Volume of Blood Collected

A total of approximately 123 mL of blood will be collected during the screen and Primary study period and approximately 120 mL blood will be collected during the Extension study. Refer to the study laboratory manual for required blood draw volumes for each test at all time points.

14.5 Handling, Shipping, Storage and Analysis of Plasma

Please refer to the Laboratory Procedures Manual for the handling of blood and plasma samples. Participant plasma specimens collected during this study may be stored for up to 15 years and used to further the knowledge of CT1812.

15 SAFETY ASSESSMENTS

15.1 Assessment of Safety

15.1.1 Safety Oversight

A study safety monitoring committee will oversee the safety of the trial. This committee will include the study director, the study medical monitor and the study principal investigator. Safety data (lab reports, AEs) will be provided to the safety committee to review at bi-weekly intervals during the trial and the committee will at minimum, meet once quarterly to discuss trial safety data.

15.1.2 Adverse Events

Adverse events will be captured from the start of study-related procedures at Visit 1 (including diagnostic assessments or signing of the Informed Consent Form [ICF]) onward during the course of this study. Important medical events and conditions occurring prior to this period are not AEs; they will be captured within the medical chart and in the Medical History section of the Case Report Form.

15.1.3 Physical and Neurological Examination

The investigator should perform a thorough examination of all body systems (exception: genitourinary and reproductive should be symptom-directed). The neurological exam is symptom-directed and may include mental state, speech, gait/posture, arm swinging, facial movements, tongue, muscle wasting (power and tone), coordination, reflexes, and sensation.

Height should be measured at Screening only. For body weight measurements, the Investigator must ensure that the scale is properly calibrated prior to study initiation, and that the same scale is used throughout the study. Weight will be collected at each visit.

15.1.4 Medical, Surgical and Psychiatric History

Medical, surgical and psychiatric history including a current DSM-V diagnosis that would interfere with the participant's ability to participate in the study including any prior history of suicidal thoughts or behavior that are believed by the investigator to represent a current safety risk (see section 14.1.12.1).

15.1.5 Vital Signs

Vital signs include body temperature, systolic and diastolic blood pressure, pulse rate and respiration rate. Body temperature will only be recorded once daily. Blood pressure and pulse rate recordings will be made after the study patient has been sitting or semi-supine and at rest for ≥ 5 minutes.

15.1.6 12-lead Electrocardiogram

ECGs will be recorded using a digital ECG to provide machine-generated interval measurements. The Bazett formula should be utilized for QTc interval correction:

$$QT_c = \frac{QT}{\sqrt{RR}}$$

15.2 Adverse Events

15.2.1 Definitions

Adverse Event

An AE is any untoward medical occurrence in a participant or clinical investigation participant undergoing a study procedure or administration of a study drug. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug, whether or not considered related to the study drug.

Related Adverse Event

A related AE is an AE with a causality rating of possible" or "probable".

Unrelated Adverse Event

An unrelated AE is an AE with a causality rating of “unlikely” or “unrelated”.

Laboratory Abnormality

A laboratory abnormality is any clinically significant laboratory abnormality suggesting a disease or organ toxicity and which is of a severity requiring active management (i.e., changes of dose, discontinuation of drug, more frequent follow-up, medical treatment or a diagnostic investigation). Laboratory abnormalities are also considered AEs, if clinically significant.

Pretreatment Adverse Events

A pretreatment AE is any AE occurring during the pretreatment period (between informed consent and initiation of a study drug).

Post-study Adverse Event

A post-study AE is an AE occurring up to 30 days after the treatment period.

Treatment-emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are all AEs occurring during the treatment period or a pretreatment AE that worsens in intensity during the treatment period.

Treatment Period

The treatment period is the period during which a participant receives study drug (i.e., day of dosing).

Serious Adverse Event

A SAE is any untoward medical occurrence that results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect observed in any offspring of the participant conceived during treatment with the study drug or is an important medical event. See Section 13,3 for more details on SAEs.

15.2.2 Collection and Rating of Adverse Events

During the course of the study (i.e., from the signing of the ICF through the Follow-up Visit plus 30 days for any SAE) all AEs, irrespective of the relatedness to the study drug, will be collected and reported on the Adverse Event Report Form. The seriousness criteria should not be confused

with the intensity of the event. In case of an SAE, a Serious Adverse Event Report Form must be completed and transmitted to the Sponsor or designee.

Overdoses and medication errors in the presence of clinical consequences should be recorded as AEs. The clinical consequence should be reported as "[enter AE] due to overdose".

15.2.2.1 Onset Date

The onset date is the date when the first sign(s) or symptom(s) were first noted. For example, if the AE is an abnormal laboratory test (such as "platelets low"), the onset date is the date when the sample was taken. If the participant was hospitalized for meningitis, and symptoms such as fever, headache and nausea started the day before the hospitalization, the onset date is the day symptoms presented versus day of hospitalization.

15.2.2.2 Assessment of Intensity

The intensity of each AE will be rated according to the following 3-point scale:

- **Mild:** Awareness of signs or symptoms, but no disruption of usual activity
- **Moderate**: Event sufficient to affect usual activity (disturbing)
- **Severe**: Inability to work or perform usual activities (unacceptable)

15.2.2.3 Relationship to Study Drug

The causal relationship of the study drug to an AE will be rated according to the following 4-point scale:

- **Unrelated:** Clearly and incontrovertibly due only to extraneous causes, and does not meet criteria listed under possible or probable
- **Unlikely:** Does not follow a reasonable temporal sequence from administration; may have been produced by the participant's clinical state or by environmental factors or other therapies administered
- **Possible:** Follows a reasonable temporal sequence from administration; may have been produced by the participant's clinical state or by environmental factors or other therapies administered

- **Probable:** Clear temporal association with improvement on cessation of study drug or reduction in dose. Reappears upon re-challenge or follows a known pattern of response to the study drug

15.2.2.4 Action Taken

The action taken toward the study drug in response to an AE will be listed as one of the following:

- **None:** no change in study drug dosage was made
- **Reduced:** dose of study drug was reduced
- **Discontinued** the study drug was permanently stopped

15.2.2.5 Outcome of Adverse Event

The outcome of an AE will be recorded as one of the following:

- **Recovered:** fully recovered or the condition has returned to the level observed at baseline
- **Recovered with sequelae:** resulted in persistent or significant disability or incapacity; the nature of the sequelae should be specified
- **Not yet recovered**
- **Death**

15.2.3 Adverse Event Follow-up

Adverse events requiring therapy must be treated with recognized standards of medical care to protect the health and well-being of the participant.

Any participant who has any AE (whether serious or non-serious) or clinically significant (in the Investigator's opinion) abnormal laboratory test values will be evaluated by the Investigator or a monitoring physician, and will be treated and followed up until the symptoms or values return to normal or acceptable levels, as judged by the Investigator and the Sponsor.

Adverse events that are unresolved at end of study or upon early withdrawal will be tracked at least weekly by site staff until resolution, for 30 days, or until the participant is lost to follow-up

(defined as failure to respond to three phone messages left on separate days and one certified letter requesting follow-up).

Participants will be instructed to inform site staff of any AEs occurring during the 30-day period after discharge or early withdrawal.

Any follow-up information available at the time of the participant's end of study will be included in the clinical study report.

Any SAE that is considered to be unexpected and related to the study drug occurring after the end of study should be forwarded to the Sponsor. These cases will be handled and submitted as expedited reports, but will not be included in the clinical study report.

15.3 Serious and Other Significant Adverse Events

15.3.1 Definition of a Serious Adverse Event

A serious adverse event is any untoward medical occurrence that

- **Results in death.** Death is not an event per se but rather an outcome. Note that any event resulting in a fatal outcome must be fully documented and reported, including deaths that occur within 30 days after treatment ends and irrespective of the causal relationship to the study drug.

- **Is life-threatening.** Life-threatening refers to an AE in which the participant was at immediate risk of death at the time of the event. It does not refer to an event, which may have caused death, if it was more severe.

- **Requires in-patient hospitalization or prolongation of existing hospitalization.** Hospitalization means that the participant was admitted to hospital or that existing hospitalization was extended as a result of an event. Hospitalization describes a period of at least 24 hours. Over-night stays for observation; stays at the emergency room or treatment on an outpatient basis do not constitute a hospitalization. However, medical judgment must always be exercised and, when in doubt, the case should be considered serious (i.e. if the case fulfills the criterion for a medically important event). Hospitalization for administrative or social purposes does not constitute an SAE. Hospital admissions and/or surgical operations planned before study inclusion are not considered AEs if the illness or disease existed before the participant were enrolled in the study, provided that the condition did not deteriorate during the study.

- **Results in persistent or significant disability/incapacity.** Disability/incapacity means a substantial disruption of a person's ability to conduct normal life functions. If in doubt, the decision should be left to medical judgment by the Investigator.

- **Is a congenital anomaly/birth defect.** Any congenital anomaly or birth defect observed in any offspring of the participant conceived during treatment with the study drug.

- **Is an important medical event.** Important medical events are events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of important medical events include AEs that suggest a significant hazard, contraindication or precaution, occurrence of malignancy or development of drug dependency or drug abuse. Medical and scientific judgment should be exercised in deciding whether events qualify as medically important.

An AE caused by an overdose or medical error is considered serious if a criterion listed in the definitions above is fulfilled.

The following are <u>not</u> considered SAEs:

- A pre-existing condition that is present prior to or at the start of the study that did not worsen

- Hospitalizations for treatment which were elective or preplanned, for a pre-existing condition unrelated to the indication under study that did not worsen

- Admission to a hospital or other institution for general care, not associated with any deterioration in condition.

15.3.2 Serious Adverse Event Reporting by the Investigator to the Sponsor

Any SAE that occurs after a participant has entered the study, whether or not related to study drug, must be reported to the Sponsor or the Sponsor's agent immediately (within 24 hours) via telephone or facsimile. If initially reported via telephone, this must be followed-up by a facsimile of the written SAE report. The Investigator must report all SAEs occurring from the time the participant signs the ICF until 30 days after last treatment with the study drug.

A completed Serious Adverse Event Report Form with the best possible details must be transmitted to the Sponsor representative by facsimile within 24 hours of knowledge of the SAE according to contact details as specified below:

Sponsor Representative and Contact Information for SAE Reporting:

15.3.3 Handling of Follow-up Information

Follow-up information may be required or additional information may be received by the Sponsor (e.g., evolution of the SAE, other signs or symptoms, final diagnosis, final outcome, hospital discharge summary, or autopsy report). The same procedures and timelines as for initial reporting, listed above, should be followed for any follow-up information. If necessary, the study site will be visited to collect additional information.

Follow-up information is required on all SAEs until one of the following criteria is satisfied:

- The final outcome of the case is known
- The event is resolved or the medical condition of the participant is stabilized
- No further information is available
- Sponsor assessment has been finalized

15.3.4 Reporting and Follow-up of Pregnancy

When an Investigator becomes aware of the pregnancy of a female participant, the Investigator must withdraw the participant from the study and follow the pregnancy until termination or until the child is 1 month old. The pregnancy will be reported immediately by telephone and by faxing a completed Pregnancy Report to the Sponsor within 24 hours of knowledge of the event. The pregnancy will not be processed as an SAE; however, the Investigator should notify the Sponsor or the Sponsor's agent of the outcome of the pregnancy by submitting a follow-up Pregnancy Report. Additionally, if the outcome of the pregnancy meets the criteria for immediate

classification of an SAE (e.g., spontaneous or therapeutic abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator will report the event by phone and by faxing a completed SAE Report Form to the Sponsor within 24 hours of knowledge of the event.

15.3.5 Expedited Reporting of Serious Adverse Events

15.3.5.1 Responsibilities

The Sponsor is responsible for ensuring the timely reporting of SAEs to Regulatory Authorities and all Investigators who participate in the clinical development program of the study drug. It is the responsibility of the Investigator to provide the Sponsor with the case information such that reporting timeline demands of applicable Regulatory Authorities can be met.

15.3.5.2 Expedited Reporting

All AEs that are serious, unexpected, and considered related to the study drug judged by either Sponsor or the Investigator require expedited reporting. All available information relevant to the evaluation of the SAE will be reported. Serious adverse events will be considered reportable regardless of whether or not the study drug was used in accordance with the provisions in the protocol.

Adverse events which are serious, but expected, or those which are not associated with the study drug will only be participanted to expedite reporting if they are required to be reported to an authority according to national requirements.

15.3.5.3 Timelines

Fatal or life-threatening serious unexpected related cases require rapid reporting. Regulatory Authorities shall be notified as soon as possible but no later than 7 calendar days after first knowledge by the Sponsor representative, followed by as complete a report as possible within 8 additional calendar days.

Serious unexpected related cases that are not fatal or life-threatening must be submitted as soon as possible, but no later than 15 calendar days after first knowledge by the Sponsor representative that the case meets the minimum criteria for expedited reporting.

It is the responsibility of the Investigator to support Sponsor activities needed to meet the aforementioned timelines for Regulatory Authority reporting in the event of an SAE.

16 AFFECTIVE AND COGNITIVE MEASURES

16.1 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS (Posner et al, 2011) is a questionnaire that assesses current and prior suicidal ideation, behavior, and attempts, along with occurrence, severity, and frequency of suicide-related thoughts and behaviors. The “Baseline/Screening” version is used for the initial visit, and the “Since Last Visit” is used for subsequent assessments.

16.2 Mini Mental State Exam (MMSE)

The MMSE (Folstein et al, 1975) is a brief clinical cognitive examination commonly used to screen for AD and other dementias. The MMSE evaluates orientation, memory, attention, concentration, naming, repetition, comprehension, and ability to create a sentence and to copy two overlapping pentagons. The scoring range is 0-30, and a lower score indicates more cognitive impairment. In this study the “WORLD backwards” version of the MMSE will be administered. The MMSE will be given at screening to determine eligibility for the trial.

16.3 Alzheimer's Disease Assessment Scale-Cognition Subscale (ADAS-cog)

The ADAS-cog (Mohs et al, 1997) is a psychometric instrument that assesses multiple cognitive domains, including memory, comprehension, praxis, orientation, and spontaneous speech. A higher score indicates more impairment; a positive change indicates cognitive worsening. The ADAS-cog has been the primary cognitive instrument in previous and ongoing Alzheimer's Disease Clinical Study (ADCS) trials. The person administering this test cannot also administer the CDR-SB.

16.4 Geriatric Depression Scale (GDS)

The GDS (Yesavage et al, 1983) is a clinician-rated instrument, which has been used in dementia as a diagnostic screen for depression and to enumerate depressive symptoms. The participant is typically interviewed alone; however, in some cases an informant may be interviewed in surrogate. For this study, the interview will be conducted with the participant.

16.5 Neuropsychological Test Battery (NTB)

The NTB (Harrison et al, 2007) is a neuropsychological test battery that in this study includes Trails A & B, Digit Span, and Category Fluency. The NTB may be more sensitive than the ADAS-Cog in assessing patients with mild to moderate AD and may have particular utility in drug studies.

16.6 Alzheimer's Disease Clinical Study – Clinician Global Impression of Change (ADCS-CGIC)

Global ratings provide verification that the effects of a treatment are readily observable and clinically meaningful. The ADCS-CGIC (Schneider et al, 1997) was developed to provide a valid and reliable global instrument for use in clinical trials. In the present proposal we will use as our global outcome measure the ADCS-CGIC, which regard as the best-validated global change instrument.

16.7 Alzheimer's Disease Clinical Study – Activities of Daily Living (ADCS-ADL)

The ADCS-ADL (Galasko et al, 1997) is a 23-item questionnaire developed by the ADCS to assess the ability to perform activities of daily living (ADLs) by participants with AD88. Using a structured interview format, study partners are queried as to whether participants attempted each item in the inventory during the prior 4 weeks and their level of performance. The ADCS-ADL scale discriminates well between normal participants and those with AD and it has good test-retest reliability. The ADCS-ADL includes some items from traditional basic ADL tests (e.g., grooming, dressing, walking, bathing, feeding, toileting) as well as instrumental (complex) activities of daily living (e.g., shopping, preparing meals, using household appliances, keeping appointments, reading).

16.8 Clinical Dementia Rating Scale – Sum of the Boxes (CDR-SB)

The CDR-SB Scale (Morris, 1993) is a clinician-rated dementia staging system that tracks the progression of cognitive and functional deterioration. Scores are on a scale of 0 through 3, with 0=no dementia, 0.5=questionable dementia, 1=mild dementia, 2=moderate dementia, and 3=severe dementia. Cognitive and functional abilities that are assessed are Memory; Orientation; Judgment and Problem Solving; Community Affairs; Home and Hobbies; and Personal Care. Memory is considered as the primary driver for scoring and the other categories are secondary

17 STATISTICAL METHODS

17.1 General Overview of the Statistical Analysis Plan

Individual data for all enrolled participants will be presented in data listings, sorted by participant and dosing arm.

17.2 Number of Participants Chosen for This Study

Approximately 21 participants will be recruited to the study (7 assigned to CT1812 300 mg, 7 assigned to CT1812 100 mg, and 7 assigned to placebo).

17.3 Analysis Populations

The safety analysis set will include all participants who were administered the investigational product (IP), including those who may have withdrawn prior to study completion. The full analysis set (FAS) for efficacy will include all subjects who receive IP and who have at least one post-dose efficacy assessment of any of the cognitive and clinical endpoints. The per protocol pharmacokinetic (PK) population will include all participants who receive IP that have no major protocol violations that impact pharmacokinetics. The per protocol pharmacodynamics analysis set will include all subjects who receive IP and who have at least one post-dose result for any CSF concentration.

17.4 Data Analysis

All descriptive statistical analyses will be performed using SAS statistical software (Version 9.3 or higher), unless otherwise noted. AEs will be assessed by the investigator for severity and will be coded for summarization using Medical Dictionary for Regulatory Activities (MedDRA® Version 10.1 or higher). Concomitant medications will be coded using WHO Drug Dictionary (enhanced) Format C, 15 Aug 2005 or more recent updated version.

Adverse events will be summarized by system organ class and preferred term, for each dose group (including placebo) and the incidence compared. Laboratory measures will be summarized by treatment group and time-point both as absolute values and as change from baseline, with descriptive statistics summarizing each group and time point. Similar presentation will be used for vital signs and for ECG interval measurements, and changes from pre-treatment baseline.

Distribution of the data will be characterized, followed by the most appropriate parametric or nonparametric procedures. Comparability of the treatment and placebo groups with respect to

demographic characteristics will be assessed. Appropriate safety tabulations and comparisons across treatment groups will be prepared.

Change from baseline in the composite scores, certain clinical outcome measures, and certain imaging parameters will be analyzed using a mixed model for repeated measures (MMRM), with treatment group as the main effect, visit, baseline score, and treatment by visit as an interaction term. The primary analysis will include post-baseline visits up to Month 6. For scales and parameters with Month 12 data, the model may be run a second time with data through the Month 12 visit. Additional covariates will be considered and will be detailed in the final SAP.

The analysis methodology described above will be used to perform the following comparisons:

- Pooled analysis: for the outcome of interest, the low and high CT1812 dosed groups will be pooled and compared with the placebo group.
- Analysis by arm: for the outcome of interest, each separate CT1812 dose group and placebo group will be compared.

For parameters with only post-baseline visit, an analysis of covariance model (ANCOVA) with treatment group as the main effect and baseline score will be run in place of the MMRM model.

Pearson correlation coefficients will be used to assess associations between imaging endpoints, CSF biomarkers and cognitive and behavioral changes (ADAS-11, ADAS-13, ADAS-14, Cognitive Composite, Memory Composite, Executive Function Composite, Attention Composite, NTB individual items, MMSE, CDR-SB, ADCS-ADL, and ADCS-CGIC). Correlations will be calculated for baseline imaging and biomarker values and baseline efficacy measures. Additionally, correlations between change from baseline in by-visit imaging and biomarker values and change from baseline in efficacy scales will be calculated. Refer to the final SAP for additional details.

17.5 Power Analysis

Computation of sample size in this within-participant design was based on estimates of the magnitude of reductions in synaptic density from post-mortem AD data of 25-45%. It is assumed that, on average, there is 30% loss of synapses in this population, and that CT1812 will restore one third of those synapses, with no change in synaptic density in the placebo group. Based on the excellent test/retest reliability of ^{11}C-UCB-J, it is conservatively assumed that there will be 10% variability in baseline and post-treatment ^{11}C-UCB-J binding potential non-displaceable (BP_{ND}) measurements.

Power is first computed by assessing whether the change in synaptic density would be larger in the treated group than the placebo group. For group sizes of 7 per group, we have ~68% power for comparison of the combined treatment of N=14 CT1812 vs. 7 placebo subjects (α = 0.05, 1-tailed test). Higher power is present in the one-sample test of the treatment group, i.e., does synaptic density increase following CT1812 treatment. In that case, a group size of 7 CT1812 patients yields 80% power to detect an increase in synaptic density. Power for detecting changes in ^{18}F-FDG is likely to be lower since the magnitude of change in the SV2A signal in AD will be larger than that of ^{18}F-FDG (20%)(Landau et al, 2012).

17.6 Clinical Outcomes

Clinical outcome measures will include: ADAS-Cog11, ADAS-Cog13, ADAS-Cog14, NTB, ADCS-ADL, MMSE, CDR-SB, and ADCS-CGIC, which will be obtained at baseline and after 24 weeks of treatment. ADAS-Cog14 will assess multiple cognitive functions including mazes and delayed recall[66] and along with the other clinical outcomes, will be used to correlate changes in synaptic density, glucose metabolism, and cognitive function following CT1812 treatment. Composite z-score scales (Cognitive Composite score; Memory composite score; Attention composite score; Executive Function composite score) will be derived from the clinical outcome measures.

Change from baseline in the composite scores and certain clinical outcome measures will be analyzed using the MMRM model described in section 17.4. For ADCS-CGIC the effect of treatment assignment will be analyzed using the same MMRM model. A Cochran-Mantel-Haenszel will also be considered and further details will be given in the final SAP.

17.7 Plasma CT1812 and CSF biomarker analysis

In addition to measuring concentrations of CT1812 in plasma and CSF, as well as CT1812 metabolites in plasma, we will also measure other CSF biomarkers associated with Alzheimer's disease (including CSF Aβ 40, Aβ 42, Aβ oligomers, tau, phospho-tau, neurogranin, synpatosomal-associated protein-25 (SNAP25), synaptotagmin and NFL. Additional CSF biomarkers are listed in the statistical analysis plan.). Change from baseline in these parameters will be analyzed using the ANCOVA model described in section 17.4.

17.8 Imaging Analysis

17.8.1 ^{11}C-UCB-J Data

For ^{11}C-UCB-J, the primary imaging outcome measure is *DVR* as produced by the Simplified Reference Tissue Model (SRTM2) using dynamic scan data from 0 to 60 min and the whole cerebellum as a reference region. For *DVR*, a composite region will be determined, including: prefrontal, lateral temporal, posterior cingulate/precuneus, anterior cingulate, lateral parietal, medial temporal, and lateral occipital regions. For the ^{11}C-UCB-J DVR outcome composite region the primary model will be analyzed without reference to age and ApoE4 status, however additional models will be run that include age and ApoE4 status as sensitivity analyses. Analyses will also be conducted to assess the relationship of age and ApoE4 status with dependent DVR variable and to determine if there is any imbalance on these variables between the treatment groups.

Regional analyses will first focus on the hippocampus since the recent cross-sectional study has shown this to be the region of largest group differences in synaptic density when comparing a group of participants with AD to healthy participants.

Individual exploratory regions include:

- Hippocampus
- Entorhinal cortex,
- Parahippocampal cortex,
- Amygdala,
- Fusiform gyrus,
- Lingual gyrus,
- Inferior/middle temporal cortex,
- Anterior cingulum,
- Posterior cingulum,
- Precuneus,
- Prefrontal cortex,
- Superior temporal cortex,
- Lateral parietal cortex,
- Lateral occipital cortex,
- Pericentral cortex, and
- Medial occipital cortex

17.8.2 ^{18}F-FDG Data

For ^{18}F-FDG, the primary imaging outcome measure is the *SUVR* from 60-90 min post injection using whole cerebellum as a reference region. For *SUVR*, a composite region will be determined, including: prefrontal, lateral temporal, posterior cingulate/precuneus, anterior cingulate, lateral parietal, medial temporal, and lateral occipital regions.

Individual exploratory regions include:

- Hippocampus
- Entorhinal cortex,
- Parahippocampal cortex,
- Amygdala,
- Fusiform gyrus,

- Lingual gyrus,
- Inferior/middle temporal cortex,
- Anterior cingulum,
- Posterior cingulum,
- Precuneus,
- Prefrontal cortex,
- Superior temporal cortex,
- Lateral parietal cortex,
- Lateral occipital cortex,
- Pericentral cortex, and
- Medial occipital cortex

17.8.3 Intrinsic Connectivity Contrast (ICC)

For resting state functional MRI, the outcome will be ICC. With this approach a map of the total connectivity of each voxel to all other voxels is computed. For ICC, a composite region of AD affected brain regions will be determined, including: prefrontal, lateral temporal, posterior cingulate/precuneus, anterior cingulate, lateral parietal, medial temporal, and lateral occipital regions.

Individual exploratory regions include:

- Hippocampus
- Entorhinal cortex,
- Parahippocampal cortex,
- Amygdala,
- Fusiform gyrus,
- Lingual gyrus,
- Inferior/middle temporal cortex,
- Anterior cingulum,
- Posterior cingulum,
- Precuneus,
- Prefrontal cortex,
- Superior temporal cortex,
- Lateral parietal cortex,
- Lateral occipital cortex,
- Pericentral cortex, and
- Medial occipital cortex

17.8.4 Volumetric MRI data

A composite region of AD affected brain regions will be determined, including: prefrontal, lateral temporal, posterior cingulate/precuneus, anterior cingulate, lateral parietal, medial temporal, and lateral occipital regions. An additional, cerebral cortex region will be included.

Individual exploratory regions include:

- Hippocampus
- Entorhinal cortex,

- Parahippocampal cortex,
- Amygdala,
- Fusiform gyrus,
- Lingual gyrus,
- Inferior/middle temporal cortex,
- Anterior cingulum,
- Posterior cingulum,
- Precuneus,
- Prefrontal cortex,
- Superior temporal cortex,
- Lateral parietal cortex,
- Lateral occipital cortex,
- Pericentral cortex, and
- Medial occipital cortex
- Lateral ventricles

17.9 Missing, Unused and Spurious Data

No imputation will be applied for missing data. Only non-missing values will be used for analyses.

18 STUDY MANAGEMENT

18.1 Protocol Amendment and Protocol Deviation

18.1.1 Protocol Amendment

Administrative amendments to the protocol will be classed as amendment of typographical errors, clarifications of confusing wording, and other minor modifications including but not limited to name, address, and contact information changes that have no impact on the safety of the participant or the science of the study. Administrative amendments will be submitted to the Institutional Review Board (IRB) for information only. The Sponsor will ensure that acknowledgement is received and filed. Otherwise, an amendment will be classed as a substantial amendment and will be submitted to the appropriate Regulatory Authorities and the IRB for approval.

18.1.2 Protocol Deviations

No deviations from the protocol are anticipated. Requests for deviations must be made in advance with the Sponsor. Should a non-anticipated protocol deviation occur, the Sponsor must be informed as soon as possible. All deviations and the reasons for the deviation will be documented by the Investigator or designated staff. Reporting of protocol deviations to the IRB and in accordance with applicable Regulatory Authority mandates is an Investigator responsibility.

18.1.3 Protocol Waivers

Protocol waivers will not be granted by the Sponsor in this study.

18.2 Ethics and Regulatory Aspects

18.2.1 Ethical Conduct of the Study and Regulatory Guidelines

To ensure the ethical conduct of this clinical study, each Investigator is expected to conduct the study in accordance with the protocol; the United States IND regulations specified under 21 CFR 11, 50, 54, 56, and 312; the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP); and the Guidelines of the Declaration of Helsinki. The Investigator will conduct all aspects of the study in accordance with all national, state and local laws of applicable Regulatory Authorities.

The responsibilities of the Sponsor, the Monitor and the Investigator will be as defined in the ICH GCP consolidated guideline, and applicable regulatory requirements in the country where the

study takes place. The Investigator is responsible for adhering to the GCP responsibilities of Investigators, for dispensing the study drug in accordance with the approved protocol or a signed amendment, and for its secure storage and safe handling throughout the study.

18.2.2 Institutional Review Board and Regulatory Approval

The study protocol and any amendments will be reviewed by an Independent Review Board. The IRB will review the written participant information sheet and the ICF, their updates (if any), and any written materials given to the participants. A listing of the membership of the IRB consulted and the name of the committee chair(s) or IRB registry (accreditation) number will be documented within the Investigator File and Trial Master File of the Sponsor.

The Regulatory permission to perform the study must be obtained in accordance with applicable regulatory requirements. All ethics approvals must be obtained and regulatory obligations met before a participant is exposed to any study-related procedure, including screening tests for eligibility.

18.2.3 Participant and Caregiver or Study Partner Informed Consent

Potential participants and their caregiver or study partner will be informed about the study both verbally and in writing. Each participant and his/her caregiver or study partner will be provided with a written participant information sheet that has been approved by the IRB and will be given a reasonable time to consider the study and to ask any questions they have regarding the study. The caregiver or study partner will consent to providing information about the participant, managing drug administration, and attending all clinic visits. The written participant information sheet and ICF must be in a language that the participant can understand.

Only the Investigator, a medically qualified Sub-investigator or a suitably qualified and trained authorized person may be involved in the informed consent process.

The Investigator or their suitable designee will obtain a freely given, written consent from each participant and his/her caregiver or study partner after an appropriate explanation of the aims, methods, potential hazards, and any other aspects of the study which are relevant to the decision of the participant to participate. The Investigator will explain that the participant is completely free to refuse to enter the study or to withdraw from it at any time, without any consequences for their further care and without the need to justify.

The ICF and caregiver or study partner consents must be signed and dated by the participant and caregiver or study partner before exposure to any study-related procedure, including screening

tests for eligibility. The participant and caregiver or study partner will receive copies of the written participant information sheet and the ICF and caregiver or study partner consent form.

Each participant will be informed that a Monitor, a Quality Assurance Auditor mandated by the Sponsor, or a Health Authority Inspector, in accordance with applicable regulatory requirements, may review his or her source records and health data. Data protection will be handled in compliance with national and local regulations.

If new safety information becomes available and results in significant changes in the risk to benefit assessment, the written participant information sheet will be revised or updated where necessary. Under these circumstances, all participants (including those already being treated) should be informed of the new information, given a copy of the revised form and allowed to reevaluate their consent to continue in the study.

18.3 End of Study and Regulatory Notification

The study can be terminated in part or in whole at the discretion of the FDA, an applicable Regulatory Authority or the Sponsor.

At the end of the study, the IRBs and Regulatory Authorities will be notified by the Sponsor according to applicable Regulatory requirements.

18.4 Data Protection and Confidentiality

The confidentiality of records that could identify participants should be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirement(s).

18.5 Monitoring

The study will be monitored to ensure that the study is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements.

On-site visits will be made at appropriate times during the study. Monitors must have direct access to source documentation in order to check the consistency of the data recorded in the CRF.

The Investigator will make available to the Monitor source documents, medical records, and source data necessary to complete CRFs. In addition, the Investigator will work closely with the Monitor and, as needed, provide them appropriate evidence that the conduct of the study is being done in accordance with applicable regulations and GCP guidelines.

18.6 Quality Assurance and Quality Control

The Sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, and reliability of the study data presented to the Sponsor lies with the Principal or Qualified Investigator generating the data.

Prior to the study initiation, the Sponsor will explain the protocol, Investigator's Brochure, and CRFs to Investigators. In addition, the Monitor will be available to explain applicable regulations and to answer any questions regarding the conduct of the study.

At its discretion, the Sponsor may conduct audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, Standard Operating Procedures, GCP, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions.

The study center may also be compelled to an inspection by a Regulatory Authority.

18.7 Source Data

Source data are defined as information in original records and certified copies of original records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study.

Source documents are the original data, documents, and records. Examples include hospital records, laboratory reports, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, other radiographic depictions or displays, participant files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study. All source documents must be reviewed by the PI and the sponsor (or designee) for compliance with GCP.

Study-specific data sheets may be used to document source information that would not normally be collected and documented in the routine management of the participant. Data sheets used for source documentation must be verified and signed by the Investigator or a delegated study site team member and must be stored and archived in the participant's clinic records (preferably) or in the Investigator File.

The Investigator will permit study-related monitoring, audit(s), IRB review(s), and regulatory inspection(s), with a direct access to all the required source documents and associated records.

19 DATA AND RECORD KEEPING

19.1 Case Report Forms

All data will be captured on 3-part carbonless paper and will be entered by the site staff and all queries will be addressed via PDF forms sent to sites via e-mail for resolution and sign-off. Cognition's data management team will employ double data entry. Standard procedures (including following data review guidelines, manual clinical review based on participant profiles, computerized validation to produce queries, and maintenance of an audit file which includes all database modifications) will be followed to ensure accurate data. Clinical personnel will review all data listings for outliers, data inconsistencies, and spelling errors.

During the course of the study, a study monitor (Clinical Research Associate) will make site visits to review protocol compliance, and review individual participant's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements.

The review of medical records will be performed in a manner to ensure that participant confidentiality is maintained. Checking source documents is required to monitor the progress of the study. Direct access to source data is also required for inspections and audits, and will be carried out giving due consideration to data protection and medical confidentiality.

19.2 Record Keeping

Study records and source documents need to be preserved for at least 15 years after the completion or discontinuation of/withdrawal from the study or 2 years after the last approval of a marketing application of CT1812 in an ICH region, whichever is the longest time period. The sponsor will be notified prior to the planned destruction of any study related source documents.

20 FINANCING AND INSURANCE

Financial aspects of the study are addressed in a separate clinical study agreement.

The Investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice. The Sponsor will provide insurance coverage for the clinical study as required by national regulations.

21 USE OF DATA AND PUBLICATION POLICY

Both the use of data and the publication policy are detailed within the clinical study agreement.

The Investigator should be aware that intellectual property rights (and related matters) generated by the Investigator and others performing the clinical study will be participant to the terms of a clinical study agreement that will be agreed between the Institution and the Sponsor or their designee. With respect to such rights, the Sponsor or their designee will solely own all right and interest in any materials, data and intellectual property rights developed by the Investigator and others performing the clinical study described in this protocol, participant to the terms of any such agreement. In order to facilitate such ownership, the Investigator will be required to assign all such inventions either to the Institution where the study is conducted or directly to the Sponsor or their designee, as will be set forth in the clinical study agreement. This agreement will not preclude the reporting of any required data to Regulatory Authorities.

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23 APPENDICES

Appendix A – Prohibited Medications

Appendix B - Prohibited Medications - Cytochrome P450 Drug Interaction Table

Appendix A – Prohibited Medications

Use of below restricted medications within 4 weeks of screening visit and during the course of the study. Exceptions to the list of excluded medications may be made on a case-by-case basis if discussed and approved by the medical monitor in advance.

- Antipsychotic agents (except risperidone ≤1.5 mg/day, quetiapine ≤100 mg/day, olanzapine ≤5 mg/day, and aripiprazole ≤10 mg/day)
- Antiepileptics (except lamotrigine, gabapentin and pregabalin for nonseizure indications))
- Centrally active anti-hypertensive drugs (e.g., clonidine, l-methyl dopa, guanidine, guanfacine, etc.)
- Sedatives or anxiolytics; use of short- to medium-acting benzodiazepines for treatment of insomnia is permitted, however, use of sedatives or hypnotics should be avoided for 8 hours before administration of cognitive tests.
    - Low dose lorazepam may be used for sedation prior to MRI scan for those patients requiring sedation. At the discretion of the investigator, 0.5 to 1 mg may be given orally prior to scan with a single repeat dose given if the first dose is ineffective. No more than a total of 2 mg lorazepam may be used for the MRI scan.
- Opiate analgesics
- Systemic corticosteroids
- Mood stabilizers (e.g., valproate, lithium);
- Moderate to strong inhibitors or inducers of CYP3A4. See Appendix B for a complete list of restricted medications.
- All hormonal contraceptives and hormone replacement therapies (oral, injectable, transdermal or implanted)
- Calcium channel blockers (verapamil and diltiazem)
- Calcium supplements greater than 1300 mg per day
- Furosemide (Lasix®)
- Coumadin®
- Digoxin

Inability to separate dosing by at least 6 hours (before or after) of CT1812 from participant medications which are sensitive or narrow therapeutic index substrates of CYP3A4, or substrates of P-gp, e.g., loperamide, vinblastine or talinolol.

Appendix B – Prohibited Medications - Cytochrome P450 Drug Interaction Table

In addition to the medications detailed in Section 9.3 (Exclusion Criteria) the following are prohibited for 4 weeks prior to screening and for the duration of the study due to interactions with cytochrome P450 or P-gp.

3A4,5,7 INHIBITORS	3A4,5,7 INDUCERS
HIV Antivirals:	Carbamazepine
indinavir	efavirenz
nelfinavir	nevaripine
ritonavir	phenobarbital
	phenytoin
clarithromycin	pioglitazone
itraconazole	rifabutin
ketoconazole	rifampin
nefazodone	St. John's Wort
erythromycin	troglitazone
grapefruit juice	
verapamil	
suboxone	
diltiazem	

Sensitive P-gp Substrate
Digoxin

From: Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). [redacted]